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ORIGINAL ARTICLES

NUTRITIONAL RECOVERY SYNDROME

Preliminary Report

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A PREVIOUS report[1] has described that undernourished children developed hepatomegaly when they begin to recover. In August 1949, 34 children of preschool age, in advanced stages of malnutrition, were admitted almost simultaneously to the Nutrition Ward of this hospital. These circumstances made it possible to study the clinical course of this group, all of whose members received the same type of treatment. The authors were able to study and systematize more carefully some clinical and laboratory aspects of the process of recovery that they have been observing for some time. This study has great importance because of the frequency with which infants and children are admitted to this hospital affected with a type of malnutrition resembling pellagra (Muñoz,[2] Benavides[3]). The present report is limited to data obtained in this first group; since then the authors have observed similar phenomena in all the undernourished children admitted to the ward.

CLINICAL MATERIAL

Thirty-four children of preschool age were studied. On admission all of them showed an advanced degree of malnutrition and loss of weight which averaged 45% of theoretic weight for age. Besides, they showed nutritional edema and pellagroid erythema, dry and scaly skin, hyperkeratosis, perifolliculitis, cheilosis, glossitis and loss of reflexes. The clinical picture is one described as "infantile pellagra."[4, 5] One of the patients included in the study is illustrated in figure 1.

Of the 34 children studied, 28 were from 2 to 5 yr. of age; 4 were younger than 2 yr. and 2 were 6 yr. of age.

During the months preceding hospitalization the patients had lived on poor diets. The sources of protein were corn, beans and a small amount of wheat; therefore the diet was deficient in lysine, tryptophane, isoleucine, valine, threonine, methionine and cystine. The biologic value of the protein mixture, calculated according to Mitchell and Block's formula,[6] was 69.7%. Moreover, this deficient diet was eaten in insufficient amounts (50% of the necessary caloric value, 20 to 60% of the normal requirement for protein).

The dietetic or nutritional value of these diets is shown in table 1.

From the Hospital Infantil, México D.F.
(Received for publication Oct. 31, 1951.)

TABLE 1

	Ingested daily	Percentage of normal requirement
Calories	700– 800	40–50%
Protein	10– 30 gm.	20–60%
Fat	5– 15 gm.	10–33%
Carbohydrate	80– 140 gm.	60–85%
Ca	100– 400 mg.	10–40%
P	200– 500 mg.	20–50%
Fe	4– 8 mg.	50–80%
Vitamin A	2000 I.U.	
Thiamine	400–1200γ	Apparently sufficient
Riboflavin	500–1500γ	Low
Nicotinic acid	1– 2.5 mg.	Low
Ascorbic acid	Less than 50 mg.	Very low

Note: Vitamins are calculated for raw foods. They were cooked slowly in water.

Methods

Therapeutic Method: The treatment consisted of a generous diet *ad libitum* which on occasion represented 200 or more cal./kg. body weight, with the addition of liver 50 gm. *ad libitum*.

This diet was as follows: breakfast, cow's milk, toast with jelly and butter, and fruit (usually bananas). At noon, soup, one egg, vegetables, toast, fruit juices and jelly. In the evening, milk, meat, potatoes, bread, butter and jelly.

The values calculated for this diet are shown in table 2.

During the first week of observation the children did not eat all the food given and no vitamins were added to the diet.

During the stage of edema and severe anemia, blood or plasma transfusions were given every other day and eventually daily, in doses no greater than 10 cc./kg. body weight.

Laboratory Methods: Serum proteins.—1. Total protein was estimated by Weichselbaum method[7] employing blood serum 0.1 cc. and using the diluted reagent.

2. A fraction formed by albumin and alpha globulin[8] was determined by Howe method[9] modified by Fierro del Río et al., using serum 0.5 cc. and Weichselbaum diluted reagent.

TABLE 2

	Amount, gm.	Prot., gm.	Fats, gm.	Carbo-hydrates, gm.	Cal.	Vit. A Units	Thia-mine, mg.	Rib. mg.	Niac., mg.	Ascorb. acid, mg.	Ca, mg.	P, gm.	Fe, gm.
Liver	50	10.0	1.5	3.0	65	4,000	0.05	0.56	2.50	3	0.52	1.85	0.0040
Milk	500	15.0	15.0	23.0	285	500	0.22	1.10	0.35	10	0.60	0.46	0.0010
Egg	50	7.0	5.0	0.0	75	500	0.12	0.20	0.02	2	0.03	0.09	0.0015
Meat	50	12.5	2.8	0.0	75	335	0.07	0.12	3.20	—	—	0.12	0.0015
Fruit	100	1.0	0.0	20.0	90	3,000	0.02	0.01	0.20	8	0.01	0.03	0.0007
Vegetables	50	1.0	0.1	5.0	25	3,750	0.07	0.25	0.12	12	0.17	0.32	0.0005
Orange juice	100	0.0	0.0	10.0	40	67	—	—	—	180	—	—	—
Potatoes	50	1.0	0.0	9.5	42	2	0.06	0.03	0.55	10	—	0.02	0.0004
Butter	15	0.0	12.0	0.0	100	750	—	—	—	—	—	—	—
Oil	10	0.0	10.0	0.0	90	—	—	—	—	—	—	—	—
Cereal	25	2.5	0.3	18.5	88	—	0.26	0.05	0.50	—	0.01	0.10	0.0010
Bread	60	6.0	0.9	36.0	152	—	0.04	0.06	0.46	—	0.01	0.06	0.0000
Sugar	35	0.0	0.0	35.0	140	—	—	—	—	—	—	—	—
Marmalade	20	0.0	0.0	15.0	60	—	—	—	—	—	—	—	—
Total		56.0	47.6	175.0	1.327	12.904	0.91	2.38	7.90	225	1.35	3.05	0.0106

3. True albumin fraction was determined by Milne method[10] modified by Fierro del Río et al., using serum 0.5 cc. and sodium sulphate in a final concentration of 26%.

4. Gamma globulin fraction was estimated by original method of Jäger and Dickerson.[11]

5. Value of alpha and beta globulins was arrived at by means of calculations based on values already determined.

Liver Function Tests.—Technics proposed by Fierro del Río and Ducci were used in determination of flocculation and thymol turbidity, employing copper sulphate in calibrating the instrument.[12, 13]

Hanger's original technic was used for cephalin-cholesterol flocculation test, employing Difco reagent and making readings at 24 and 48 hr.[14]

Liver Biopsies.—Specimens were obtained by puncture with the Silvermann needle. One piece was fixed in 10% formol and another in solution alcohol and embedded in paraffin. First piece was stained with hematoxylin-eosin and the other with Langhan's technic.[15]

Statistical Method: Means were calculated by the formula $M = \frac{\Sigma x}{n}$ where Σx represents the total sum of values and n, the number of cases studied.

Standard deviations (σ) were calculated using the formula: $\sigma = \sqrt{\frac{\Sigma x^2}{n} - M^2}$

Standard error of the mean (Es) was calculated by the formula: $Es = \frac{\sigma}{\sqrt{n}}$

Significance ratios of difference between the values found for the clinically healthy and those of the malnourished group were calculated by the formula: $C_1 = \frac{M_1 - M_2}{\sqrt{Es_1^2 + Es_2^2}}$

Ratios above 2 indicate a significant difference.[16]

Results

Clinical Findings: The signs and symptoms observed appeared in the following sequence:

1. Transient weight loss, followed by a progressive increase.

2. Edema, observed in 24 of 34 cases, which disappeared completely by 17 ± 7 days.

3. By 20 ± 11 days there was clearly perceptible hepatomegaly, the liver being palpable 2 to 4 cm. below the costal margin at the midclavicular line. The liver was, in the majority of cases, of normal consistency with a sharp edge, not deformed and not tender. Frequently the hepatomegaly was noted first in the left lobe where it was more marked.

4. At 32 ± 13 days the following clinical manifestations appeared, constituting the principal findings of the nutritional recovery syndrome:

A. More marked hepatomegaly, with persistence of the aforementioned characteristics. The liver was now palpable from 4 to 7 cm. below the costal margin.

B. Distended abdomen with soft walls, not tympanitic. The distention was such that it contributed to the production of moderate dyspnea (Figs. 2 and 3).

C. A barely apparent superficial thoraco-abdominal venous network (Figs. 4 and 5).

D. More than 50% of the cases showed ascites. Its duration was short, from 8 to 15 days.

All these phenomena were observed during the time that the patients were making a satisfactory gain in weight, as can be seen in graph 1. The signs and symptoms of the syndrome increased slightly during the following two weeks but afterwards decreased and disappeared almost completely in 85 ± 24 days. However, in a large percentage of the patients a moderate degree of hepatomegaly was still present when they left the hospital.

5. In approximately 50% of the cases at about the sixtieth day of hospitalization considerable hypertrichosis was found, more marked on the shoulders, thighs and face. This

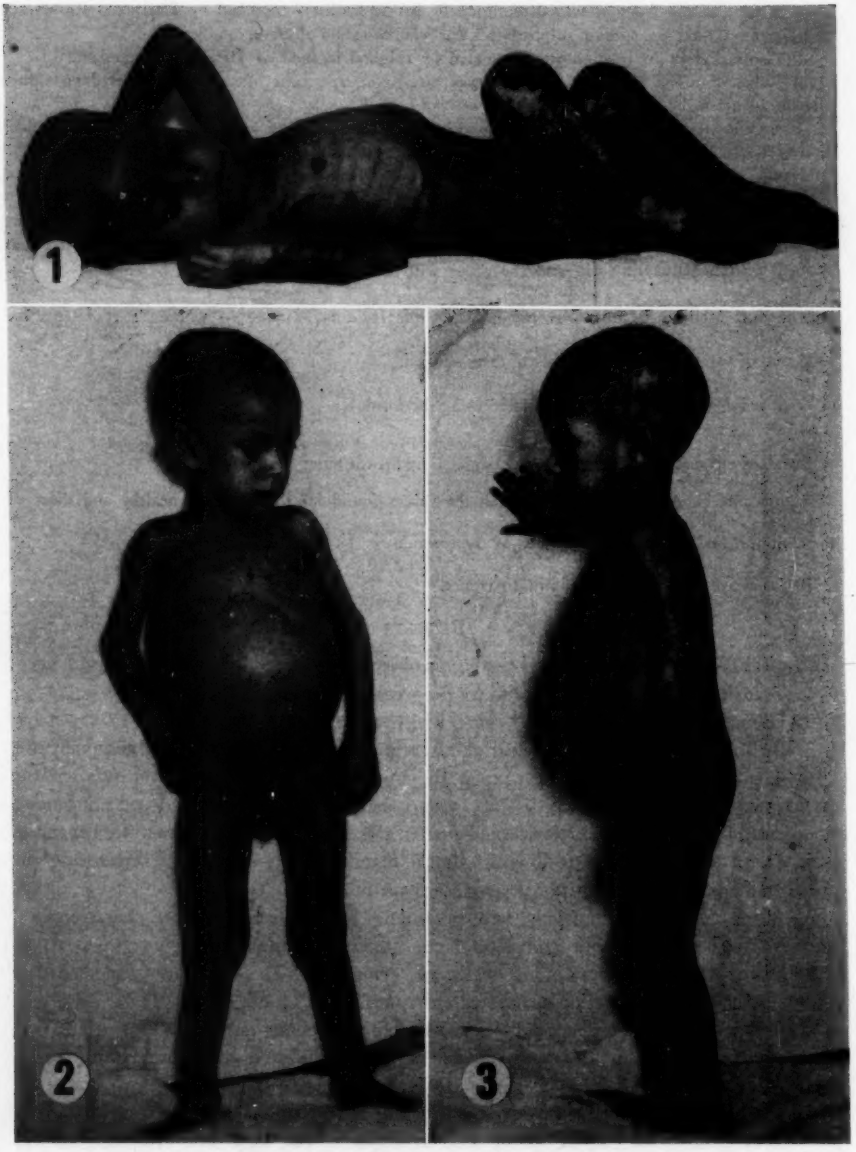


FIG. 1. Appearance of patient on admission to hospital.

FIGS. 2 and 3. Syndrome in full development.

did not exist at the time of admission. It had not disappeared when the children were discharged. In a certain number of children, the hypertrichosis on the face invaded the forehead extensively and reached the eyebrows (Figs. 6 and 7).

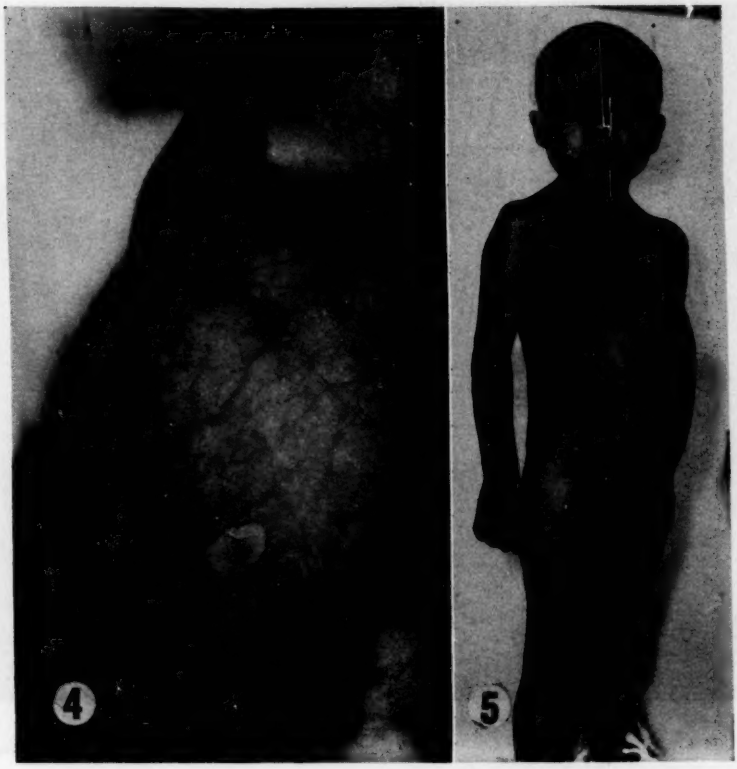


FIG. 4. Though recovery is advanced, globose abdomen and visible collateral circulation on abdominal wall are apparent.

FIG. 5. Syndrome has passed its maximum and some of its manifestations are diminishing.

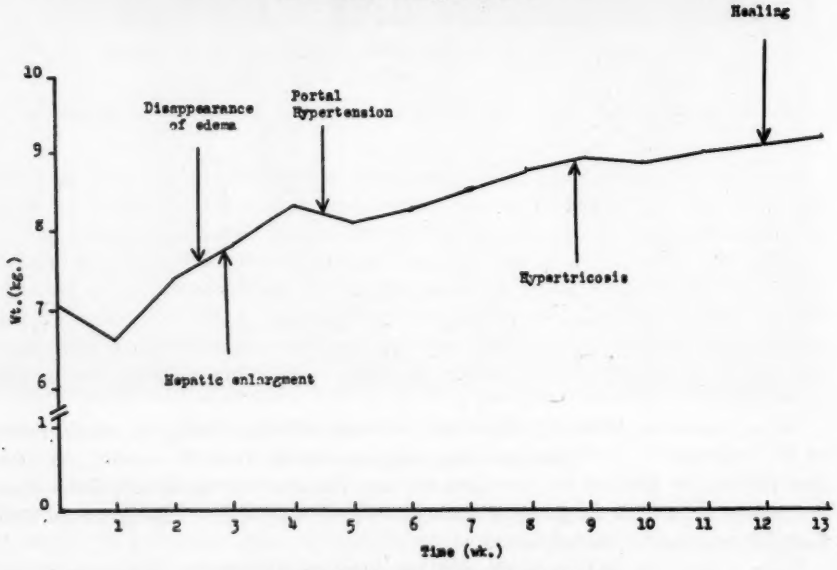
6. At the time of discharge (after three months of hospitalization) a moderate number of the patients showed an increase of the muscle masses of the thighs, contrasting with the general appearance of the patient who had not yet reached his normal weight.

Laboratory Findings: 1. Serum Protein.—Successive tables will show the figures obtained for the different protein fractions, according to determinations made at intervals of two weeks, before and after the onset of the syndrome. In order to make a correct comparison of the data obtained, they have been compared with the standards obtained in the authors' service in clinically healthy preschool age children (Gómez, Ramos and Cravioto).[17]

Table 3 shows the findings in the second two week period preceding the establishment of the syndrome. It is obvious that they differ considerably from the normal, since the total protein, the albumin and the alpha and beta globulins are significantly lower than in a healthy child while the gamma globulins are significantly higher. The figures for total globulins were within normal limits.

Table 4 gives the findings in the first two week period after the beginning of the

FIGS. 6 and 7. Hypertrichosis.



GRAPH 1. Weight increase during hospitalization.

TABLE 3

PROTEIN PATTERN OBSERVED BETWEEN 15 AND 30 DAYS BEFORE ONSET OF SYNDROME

Blood protein	Pattern in cases studied	Normal pattern	C_1*
Total protein	5.19 gm.	6.86 gm.	3.98
Albumin	2.52	3.62	5.24
Total globulin	2.94	3.31	1.00
Alpha globulin	0.64	0.96	4.57
Beta globulin	0.84	1.58	4.11
Gamma globulin	1.62	0.68	5.52

(Only the average level of each fraction has been noted without showing the standard deviation, so that the total sum of the fraction does not correspond to the total level.)

* A C_1 higher than 2 was considered statistically significant.

TABLE 4

PROTEIN PATTERN BETWEEN 1 AND 15 DAYS AFTER ONSET OF SYNDROME

Blood protein	Pattern in cases studied	Normal pattern	C_1
Total protein	7.19 gm.	6.86 gm.	1.83
Albumin	3.29	3.62	3.00
Total globulin	3.76	3.31	1.87
Alpha globulin	0.87	0.96	1.28
Beta globulin	0.95	1.58	6.30
Gamma globulin	2.06	0.68	13.80

TABLE 5

PROTEIN PATTERN OBSERVED BETWEEN 30 AND 45 DAYS AFTER ONSET OF SYNDROME

Blood Protein	Pattern in cases studied	Normal pattern	C_1
Total protein	7.33 gm.	6.86 gm.	2.13
Albumin	3.19	3.62	3.07
Total globulin	4.06	3.31	3.94
Alpha globulin	1.13	0.96	1.88
Beta globulin	0.96	1.58	4.77
Gamma globulin	1.94	0.68	7.41

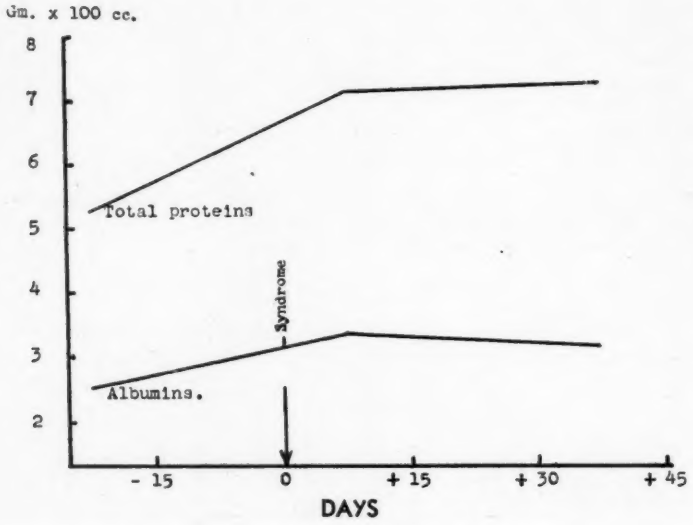
syndrome. Here the findings consisted in a greater elevation of the gamma globulin, the normalization of the total protein and the persistence of hypoalbuminemia.

Finally, in table 5 it is seen that the protein pattern of the third two week period after the onset of the syndrome also differs from that of the healthy child in that there is a decrease in the albumin and an increase in gamma globulin and in total protein.

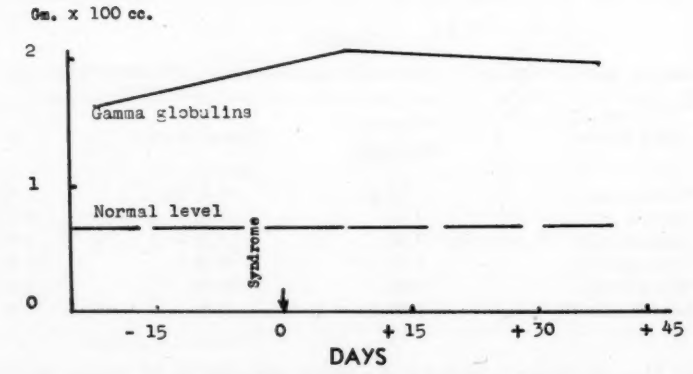
The alpha globulin, which was very low in the first determination, when edema was still present, rapidly became normal and remained so.

The fundamental characteristics of the protein pattern of this syndrome are shown in graphs 2 and 3 and in table 6 in which the statistical relationships between the first determination of gamma globulins and those made during the course of the disease are presented.

In summary, it can be said that, in regard to the blood proteins, the syndrome is char-



GRAPH 2. Changes of total proteins and albumins of plasma.



GRAPH 3. Changes of plasma gamma globulins.

acterized by profound changes in the plasma gamma globulins which are elevated far above normal, and by other changes characteristic of malnutrition such as persistent hypoalbuminemia with normal total proteins.

2. Hepatic Function Tests: The frequency with which the authors observed abnormal

thymol turbidity tests in the presence of normal cephalin-cholesterol was greater as time elapsed and the syndrome developed, as can be seen in table 7.

3. Liver Biopsies: Eighty-six liver biopsies were performed in the cases studied (table 8). Three fundamental types of lesions were reported: a. fatty metamorphosis; b. protein depletion; c. hepatitis.

The diagnosis of protein-depletion lesions were made according to Moore[18] and based on the experimental work of Elman, Smith and Sachar.[19]

TABLE 6

COEFFICIENT OF STATISTICAL SIGNIFICANCE (C_1) COMPARING GAMMA GLOBULIN LEVEL AT BEGINNING OF STUDY AND LATER

First determination (between 30 and 16 days before onset of syndrome)	Later determination	Gamma globulin	C_1
1.62 gm.%	2nd determination (between 15 and 1 days before onset)	1.93 gm.	1.30
1.62	3rd determination (between 1 and 15 days after onset)	2.06	2.44
1.62	4th determination (between 16 and 30 days after onset)	1.84	1.10
1.62	5th determination (between 31 and 45 days after onset)	1.94	1.45

TABLE 7

INCIDENCE OF ABNORMAL THYMOL TEST WITH NORMAL CEPHALIN-CHOLESTEROL TEST

Period of Determination	Incidence
Between 30 and 16 days before onset of syndrome	50%
Between 15 and 1 days before onset of syndrome	62%
Between 1 and 15 days after onset of syndrome	64%
Between 16 and 30 days after onset of syndrome	67%
Between 31 and 45 days after onset of syndrome	75%

The incidence of the more important lesions has been compared in terms of percentage distribution.

The abnormal biopsies were distributed uniformly throughout the period of study. Hepatitis was reported in approximately 75% of the abnormal biopsies, but its distribution was uniform throughout the period studied. Fatty infiltration was progressively less and the intensity of the infiltration was also gradually less. Between 40 and 60 days after the onset of the syndrome, the few reports of fatty infiltration describe the lesion as being only slight or minimal (Figs. 8 and 9).

4. Eosinophilia: According to table 9, from 60 to 75 days after the onset of the syndrome some of the patients showed a relative eosinophilia. They did not have intestinal parasites or allergy. Gómez, Frenk and Ramos[20] continued these studies by means of absolute eosinophil counts in a second group of children studied in 1950. These results were published in a separate report.

DISCUSSION

These findings constitute a definite picture appearing in preschool age children during the process of recovery from severe malnutrition. Its explanation is difficult. The authors

believe that in the pathogenesis of the picture described they have one fundamental factor: the upsetting of a metabolic equilibrium reached during long periods of starvation. This factor has been widely discussed by the Gillmann brothers[21] upon considering the importance of the addition of insufficient quantities of milk to the diet of pellagrins

TABLE 8

EVOLUTION OF LIVER LESIONS AS REPORTED BY BIOPSIES

Period when biopsies were performed	Abnormal biopsies	Fatty metamorphosis	Protein depletion	Hepatitis
Between 40 and 21 days before onset of syndrome	15.12%	40.00%	—	—
Between 20 and 1 days before onset of syndrome	15.80	17.20	14.00%	20.46%
Between 1 and 20 days after onset of syndrome	15.35	16.80	14.00	21.32
Between 21 and 40 days after onset of syndrome	18.06	14.00	23.33	21.62
Between 41 and 60 days after onset of syndrome	20.55	12.00	26.67	17.30
Between 61 and 80 days after onset of syndrome	15.12	—	22.00	19.30
	100.00%	100.00%	100.00%	100.00%

TABLE 9

RELATIVE COUNTS OF EOSINOPHILS

	Children with no parasites		Children with parasites	
	With less than 3% eosinoph.	With more than 3% eosinoph.	With less than 3% eosinoph.	With more than 3% eosinoph.
5th and 6th wk. before onset of syndrome	100%	0%	89%	11%
3rd and 4th wk. before onset of syndrome	96	4	89	11
1st and 2nd wk. before onset of syndrome	96	4	57	43
1st and 2nd wk. after onset of syndrome	94	6	38	62
3rd and 4th wk. after onset of syndrome	78	*22*	40	60
5th and 6th wk. after onset of syndrome	92	8	66	34
7th and 8th wk. after onset of syndrome	94	6	31	69
9th and 10th wk. after onset of syndrome	76	*24*	35	65
11th and 12th wk. after onset of syndrome	67	*33*		
13th and 14th wk. after onset of syndrome	84	*16*		

and other severely malnourished patients or the disastrous effects of large amounts of niacinamide on the pellagrins. In this connection Miranda[22] showed experimentally the noxious effects of vitamin concentrates added to poor diets of rats. Also one of the present authors[23] has written on the clinical manifestations of the metabolic imbalance in malnourished children.

The finding which constitutes the initial clinical basis for the syndrome consists of hepatomegaly, ascites and collateral circulation (intrahepatic portal hypertension[?]). Since the hepatomegaly cannot be due to fatty infiltration it is probably related, at least partially, to the lesions of protein depletion. It may be supposed that the protoplasm of

these cells has a protein deficiency which facilitates the binding of a considerable amount of intracellular water. The consequent swelling of the cells presses on the sinusoids and in this way establishes the intrahepatic-portal hypertension. The authors believe that the

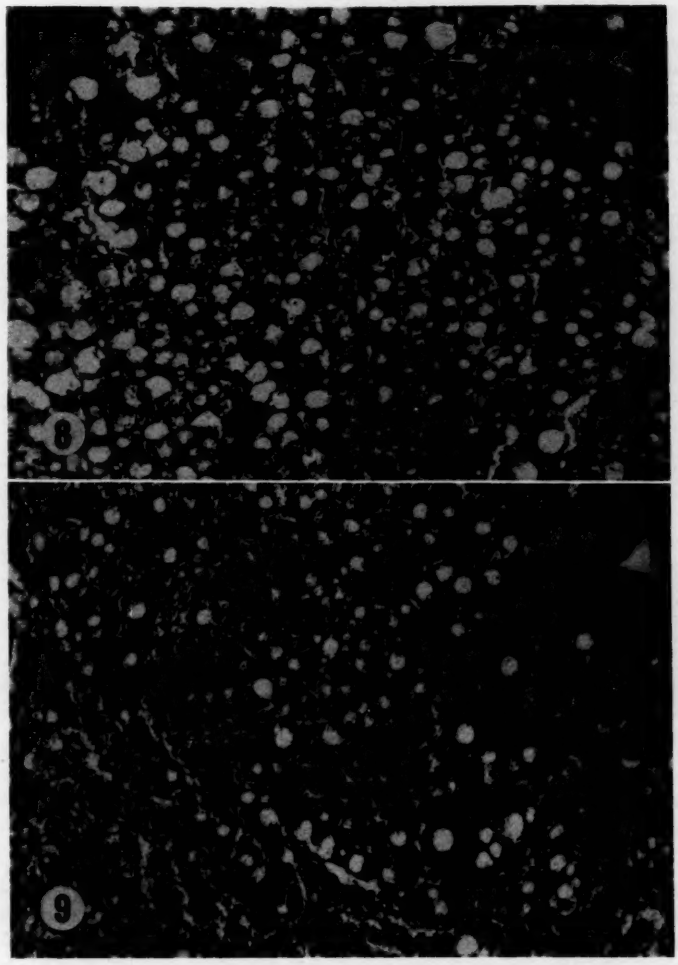


FIG. 8. Fatty liver infiltration of high degree.

FIG. 9. Fatty liver infiltration of lower degree (protein depletion shows better).

protein depletion of the hepatic parenchyma and cellular swelling becomes possible as the fat (hydrophobic material) disappears (Fig. 10).

According to Himsworth, the concomitant ascites is explained by three factors: The probable presence of an antidiuretic factor, produced in the injured liver, embarrassed portal circulation and hypoalbuminemia or, more correctly, dysproteinemia.

The finding of abnormal thymol turbidity tests in the presence of normal cephalin-cholesterol flocculation tests is very suggestive of hepatic regeneration, probably following lesions of massive necrosis as described by Himsworth. It is a well known fact that these lesions can be produced by primary nutritional deficiencies in which sulfur-containing amino acids are deficient.

The authors have demonstrated in another paper[24] that in malnourished children, abnormal thymol turbidity and abnormal cephalin-cholesterol flocculation tests occur together only in the presence of infection; that is, such findings cannot be blamed on malnutrition alone. On the other hand, an abnormal thymol turbidity test with a normal cephalin-cholesterol flocculation test is a phenomenon seen with significant frequency in cases of malnutrition and pellagra, in which it is not possible to detect any infection.

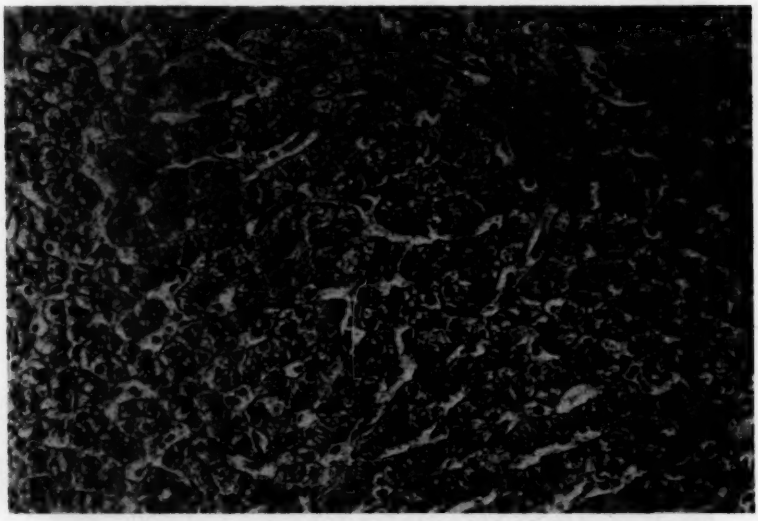


FIG. 10. Fatty liver infiltration has completely disappeared. Protein depletion images persist; they are rather numerous though cure has gone considerably forward.

In this study, therefore, the authors have included only the abnormal thymol turbidity tests and normal cephalin-cholesterol tests, checking these against definitely negative controls.

The most interesting finding in the liver biopsies was the progressively decreasing fatty infiltration. Studies of the hepatic reticulum are lacking and glycogen determinations are in progress.

Concerning the blood proteins, the series studied in these patients confirmed the impression that there is an inverse relationship between the albumins and the alpha globulins as a compensatory mechanism which among other things determines the presence or absence of edema. The fundamental phenomenon lies in the extraordinary increase in gamma globulins. Although former studies demonstrated that this increase in gamma globulin is not a specific effect of infection, there is no explanation for it.

The authors found hypertrichosis of such a peculiar density and distribution, that it must be considered as another manifestation of the process of recovery, clearly of endocrine origin. Its relation to the adrenal cortex is possible.

The number of cases with serial eosinophil counts is insufficient to come to a definite conclusion, but in the children studied there exists a certain rhythm both in the level of circulating eosinophils and in their response to adrenalin. As said before, this subject has been discussed elsewhere.

Summary

This paper presents clinical and laboratory data which indicate the development of a syndrome heretofore undescribed and still incompletely studied which appears in children during recovery from severe malnutrition.

The principal clinical findings are portal-intrahepatic hypertension beginning 20 to 40 days after treatment is instituted and lasting about a month.

Hepatomegaly, which is the first sign, is marked and progressive, affects particularly the left lobe and is inversely proportional to the degree of fatty infiltration of the liver, as is demonstrated by liver biopsies.

Along with the hepatomegaly there is distention of the abdomen, a thoraco-abdominal venous network and ascites.

Later phenomena (occurring after about 60 days of treatment) are hypertrichosis of the forehead, back and thighs, as well as a more or less marked eosinophilia not explained by intestinal parasites or allergy.

The most important chemical finding is the hyper-gamma globulinemia, the highest level of which coincides with the appearance of the portal hypertension; this is definitely statistically significant. At the same time a considerable elevation of total plasma proteins takes place and thymol turbidity tests become progressively more abnormal.

Acknowledgment

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References

1. Ramos Galván, R., La desnutrición infantíl en México: Sus aspectos estadístico clínico, dietético y social, Bol. méd. d. Hosp. Infantil **5**:804, 1948.
2. Muñoz, T. J., Aspectos clínicos de la pelagra en nuestro medio, Bol. méd. d. Hosp. Infantil **3**:404, 1946.
3. Benavides, V. L., and de la Torre, J., La desnutricion infantil, Bol. méd. d. Hosp. Infantil. **5**:311, 1948.
4. Gillman, J., and Gillman, I., Perspectives in Human Malnutrition, New York, Grune & Stratton, 1951.
5. Jolliffe, N., Tisdall, F. F., and Cannon, P. R., Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1950, p. 531.
6. Mitchell, H. H., and Block, R. J., Some relationship between amino acid content of proteins and their nutritive values for rat, J. Biol. Chem. **163**:599, 1946.
7. Weichselbaum, T. E., Accurate and rapid method for determination of proteins in small amounts of blood serum and plasma, Am. J. Clin. Path. **16**:40, 1946.
8. Dole, V. P., and Braum, Esther, Electrophoretic patterns of normal plasma, J. Clin. Investigation **23**:708, 1944.
9. Howe, P. E., Use of sodium sulfate as globulin precipitant in determination of proteins in blood, J. Biol. Chem. **49**:93, 1921.
10. Milne, J., Serum protein fractionation: Comparison of sodium sulfate method and electrophoresis, J. Biol. Chem. **169**:595, 1947.

11. Jager, B. V., and Dickerson, Margaret, Simple quantitative method for estimating gamma globulin in human serum, J. Biol. Chem. **173**:683, 1948.
12. Fierro del Río, L., Evaluación clínica de la prueba de enturbamiento del timol, Rev. méd. d. Hosp. Gral. **9**:24, 1947.
13. Ducci, H., Thymol test of MacLagan: Standardization and adaptation to Evelyn photoelectric colorimeter, J. Lab. & Clin. Med. **32**:1266, 1947.
14. Hanger, F. M., Serological differentiation of obstructive from hepatogenus jaundice by flocculation of cephalin-cholesterol emulsions, J. Clin. Investigation **18**:261, 1939.
15. Krajiar, A. A., Histological Technique, St. Louis, C. V. Mosby Company, 1940, p. 122.
16. Pearl, R., Introduction to Medical Biochemistry and Statistics, New York, W. B. Saunders Company, 1940, p. 293.
17. Gómez, F., Ramos Galván, R., and Cravioto Muñoz, J., Estudios sobre el niño desnutrido. V. Las proteínas y sus fracciones en el pre-escolar clínicamente sano y en el desnutrido, Bol. méd. d. Hosp. Infantil **7**:497, 1950.
18. Moore, R. A., Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, p. 7.
19. Elmar, R., Smith, M. G., and Sachar, L. S., Correlation of cytological with chemical changes in liver as influenced by diet, particularly protein, Gastroenterol. **1**:24, 1943.
20. Gómez, F., Frenk, S., and Ramos Galván, R., Estudios sobre el niño desnutrido. IX. Los eosinófilos circulantes y la prueba del Thorn en el pre-escolar desnutrido, Bol. méd. d. Hosp. Infantil **8**:609, 1951.
21. Gillman, J., and Gillman, T., Hepatic damage in infantile pellagra, J.A.M.A. **129**:12, 1945.
22. Tapia, M. A., and Miranda, F. P., Valoración biológica experimental de dietas vegetarianas de bajo costo, Bol. méd. d. Hosp. Infantil **5**:17, 1948.
23. Ramos Galván, R., Las desnutricíon infantil en Mexico: Sus aspectos estadístico, clínico, dietético y social, Bol. méd. d. Hosp. Infantil **6**:635, 1948.
24. Gómez, F., Ramos Galván, R., Bienvenú, Beatríz, and Cravioto Muñoz, J., Estudios sobre el niño desnutrido. IV. Pruebas del funcionamiento hepático en el pre-escolar sano y en el desnutrido, en el pelagroso y en el infectado, Bol. méd. d. Hosp. Infantil **7**:485, 1950.

SPANISH ABSTRACT

Sindrome de Recuperación Nutricional

En este trabajo se presentan hechos clínicos y de laboratorio que sustentan la existencia de un síndrome no descrito con anterioridad y aún no totalmente estudiado, que aparece durante el proceso de recuperación en los niños gravemente desnutridos.

Los principales hallazgos clínicos estriban en fenómenos de hipertensión porta-intrahepática de intensidad más o menos marcada y con duración aproximada de un mes, que aparecen de veinte a cuarenta días después de la iniciación del tratamiento.

La hepatomegalia, que es el primer signo, es intensa y progresiva, afecta mayormente al lóbulo izquierdo y guarda una relación inversa con la intensidad de la esteatosis hepática, demostrada por las biopsias de hígado. Aparejada a la hepatomegalia, está la presencia de abdomen globoso, red venoso toraco-abdominal y líquido de ascitis.

Un fenómeno tardío, es la aparición de hipertricosis en frente, cintura escapular y muslos, así como el desarrollo de eosinofilia más o menos marcada en ausencia de parasitosis intestinal o de evidencias de alergia.

El hallazgo químico más importante es la hiper-gamma-globulinemia, cuyo nivel más alto coincide con la aparación del síndrome de hipertensión porta y tiene siempre un alto grado de significación estadística. Al mismo tiempo, puede observarse la normalización de los niveles de las proteínas totales del plasma y pruebas de turbidez del timol, progresivamente más anormales.

Se insiste en que la patogenia de este cuadro no está definitivamente establecida, pero se hacen algunas consideraciones, a título de hipótesis de trabajo.

Hospital Infantil

ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS IN PREMATURE INFANTS

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THE concentrations of albumin, alpha 1, alpha 2, beta and gamma globulins determined electrophoretically on 44 serum samples from 27 premature infants ranging in age from 7 hours to 65 days are reported in this study. Although these values, obtained during the course of other studies on premature infants, should not be regarded as standards for "normal" premature infants, they are presented because so few determinations of these quantities have been published. Hence by pointing out the variations that are present and the trends with age, this study may be useful to those speculating about the electrophoretic patterns in prematures and to those contemplating more extensive studies of the components of serum proteins or wishing to investigate the factors influencing the concentration of an individual fraction.

MATERIAL AND METHODS

The 1st 14 infants were chosen from the larger premature population in the nursery merely on the basis of their doing well and the ease of obtaining nonhemolyzed samples. The last 13 infants represent all prematures with a birth weight of less than 1600 gm. who appeared well and who were not being used in other studies involving alterations in food mixtures or routine which might interfere with the present investigation. All infants were from parents in a poor economic group; 8 infants were Negroes, 1 Chinese, 9 Puerto Rican and 9 others of varied white parentage.

Weight gain of all infants was within the range of what is considered normal[1] except for one patient receiving ACTH therapy for retrolental fibroplasia. Feeding routine was an olac® food mixture (1 oz. made up to 5 oz.) supplying 120 to 160 cal./kg./day after the 1st 7 to 10 days, as previously described.[1] Two infants received whole blood transfusions 10 and 18 days, respectively, before a sample of serum for analysis was taken.

Total nitrogen values were determined by a micro-Kjeldahl method. The serum was digested with mercuric sulfate as a catalyst and the evolved ammonia absorbed in boric acid and titrated with standardized acid.[2] The serum protein was calculated from total N minus NPN multiplied by 6.25. In accordance with results of previous investigators[3-5] NPN was assumed to be 50 mg./100 cc. for 1st 5 days of life, 40 mg./100 cc. for 6th to 10th day and 30 mg./100 cc. thereafter. The use of these assumed values for NPN will not alter the true value of total serum protein appreciably. An error of 10 mg./100 cc. in NPN results in an error of only 63 mg./100 cc. in the total protein value. For electrophoretic analysis fresh nonhemolyzed serum[6] was diluted 1:3 with "veronal" buffer (0.1M sodium diethylbarbiturate—0.02M diethylbarbituric acid, pH = 8.6, M = 0.1)[7] and equilibrated by static dialysis for 16 to 20 hr. Analyses were made in a Tiselius micro cell of 2.0 cc. capacity with the Perkin-Elmer Tiselius Electrophoresis Apparatus, Model 38. Schlieren diagrams were obtained by a modification of Longsworth's scanning method.[6, 8] Each pattern was enlarged threefold photographically. The components were segregated by dropping perpendiculars to the base line[9] and the area measured with a planimeter. The data were then converted into gm./100 cc. serum from the total serum protein determination. This was done for purposes of approximation and comparison with the literature, although it is realized that some error is involved. [10, 11]

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TABLE 1

Patient No.	Sex	Birth Wt., gm.	Wt. day Bled, gm.	Age (post-partum) days	Serum Protein, gm./100 cc.	Electrophoretic Fractionation* (gm./100/cc.)				
							Globulins			
						Albumin	Alpha 1	Alpha 2	Beta	Gamma
1	F	1260	1260	7 (hr.)	6.18	3.58	.32	.65	.79	.84
			1275	7	5.68	3.75	.48	.54	.48	.42
			1525	15	5.41	3.11	.45	.63	.79	.40
			2030	29	4.95	3.09	.42	.60	.63	.23
2	F	1390	1290	2	5.73	3.27	.35	.41	1.05	.58
			1475	31	5.16	2.59	.55	.79	.71	.50
3	M	1820	1675	3	6.69	3.92	.42	.55	.54	1.19
4	F	?	1450	5	5.32	3.09	.30	.56	.71	.63
			1600	15	5.60	3.46	.25	.69	.64	.58
			2240	29	4.99	2.97	.24	.67	.70	.40
5	F	1540	1425	6	5.65	3.72	.14	.48	.53	.76
			1710	16	5.43	3.60	.20	.51	.63	.47
			2360	30	4.42	2.75	.30	.45	.58	.33
6	M	2180	2110	7	5.73	3.88	.27	.56	.53	.43
7	F	2045	2020	7	6.63	3.87	.33	.52	.65	1.25
8	F	1600	1520	8	5.61	3.89	.30	.56	.39	.44
9	M	2160	1965	9	4.68	3.11	.30	.34	.42	.51
10	F	1570	1320	9	6.69	4.33	.30	.61	.59	.85
			1625	19	6.56	3.90	.40	.61	1.00	.64
			1800	25	6.18	3.90	.25	.63	.67	.71
11	F	1750	1800	10	5.56	3.51	.30	.25	.91	.59
12	F	1780	1730	10	5.62	3.51	.29	.40	.75	.64
13	F	1600	1750	12	5.45	2.98	.31	.74	.69	.71
14	F	1330	1280	16	6.22	3.50	.42	.83	.97	.49
			1680	30	4.27	2.43	.35	.55	.65	.29
			2020	45	4.35	2.45	.45	.55	.71	.20
			2685	59	4.68	2.87	.26	.68	.70	.21
15	M	1890	2230	18	5.09	3.30	.26	.59	.59	.34
16	M	1510	1630	19	5.53	2.89	.66	.91	.62	.43
17	F	1500	1840	22	4.93	2.75	.31	.81	.67	.39
18	M	1550	1475	22	4.75	3.04	.29	.52	.44	.48
19	M	1540	1930	23	4.93	2.88	.27	.66	.55	.57
20	F	1660	1830	23	4.82	3.34	.30	.48	.39	.29
21	M	1200	1230	24	5.06	3.32	.46	.61	.52	.14
			2330	65	4.24	2.64	.58	.41	.50	.09
22	M	1560	1770	26	4.24	2.94	.26	.37	.39	.27
			2280	45	4.38	3.08	.28	.41	.45	.17
23	M	1720	2840	26	5.05	3.27	.15	.60	.59	.43
24	F	1550	1570	28	5.01	3.02	.33	.59	.53	.53
25	F	1390	1440	30	4.20	2.23	.39	.67	.49	.40
			2060	61	4.38	2.77	.34	.68	.54	.22
26	M	1275	1740	38	4.14	2.62	.34	.50	.48	.20
			2120	52	4.67	3.25	.26	.49	.46	.21
27	M	800	1950	51	4.58	2.98	.36	.44	.57	.21

* From descending boundaries.[6]

Results

Total Protein: Despite the great variations in the values for the concentration of serum proteins at any age during this study, chart 1 and table 1 show a gradual decline from around 6 gm./100 cc. during the first week of life to about 4.5 gm./100 cc. at 30 days of age. The data suggest a slight rise in values by 50 to 60 days, but the observations are too few in this region to define the trend. For these subjects there is no evident correlation between birth weight and the level of serum protein at any age during the first four weeks. The values for infants with birth weights below 1400 gm. and those over 1600 gm. are thoroughly intermixed.

Serum Albumin: The concentrations of serum albumin parallel those for total serum

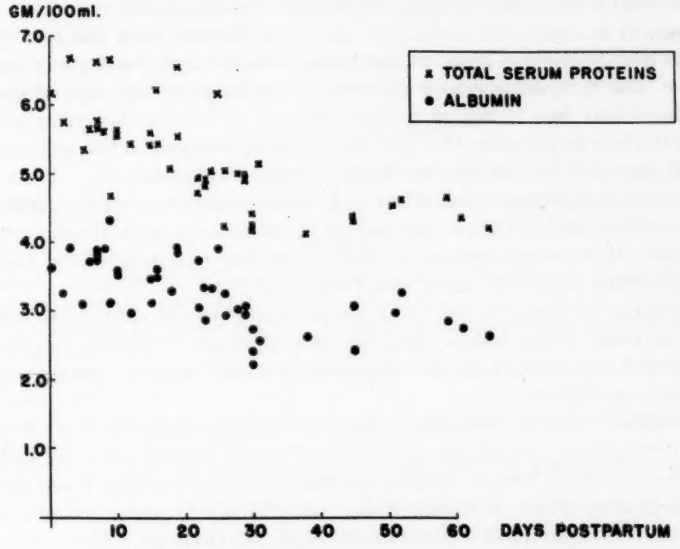

Chart 1. Concentration of serum proteins and serum albumin in premature infants.

proteins, as shown in chart 1. About two-thirds of the decline in the concentration of serum protein is due to decline in the level of serum albumin. The interval until full feedings were reached, the level of calories fed or other details in the course of the patient's care did not seem to influence the concentration of serum albumin. The authors have no data at present to evaluate the role of the immaturity of liver function, change in blood volume or rates of production or destruction of albumin in accounting for this decline in serum albumin concentration.

Alpha 1 Globulins: The concentrations of alpha 1 globulins at any age show considerable variation. Infants with birth weights below 1400 gm. tend to have slightly higher values for this fraction throughout the study. No definite trend is apparent over the 60 day period. In the few serial determinations available consecutive values may be either higher or lower than the preceding one.

Alpha 2 and Beta Globulins: The concentrations of the alpha 2 and beta globulins are

widely variable and reveal no definite trend with increasing age. There is no significant difference in these globulin levels for the smaller and larger babies.

Gamma Globulins: The concentrations of gamma globulins show a distinct decrease with increasing age from approximately 0.7 gm./100 cc. during the first week of life to about 0.2 gm./100 cc. at 40 days of age. The few determinations made show no tendency for the gamma globulins to rise by 60 days of age.

Comments

This data cannot be taken as representative of "normal" prematures for several reasons. The basis for selection of patients for this study may have introduced bias. There was no rigid control of many factors which might affect the serum proteins, except to exclude infants on other food mixtures or appearing to be ill. The distribution of the birth weights of the patients studied—26% under 1400 gm., 41% between 1401 and 1600 gm. and only 33% over 1601 gm.—is not the usual distribution of birth weights in a premature population. Due to studying infants only while in the hospital, only 20% of the values were obtained later than 30 days postpartum and none of these measurements were from infants with birth weights over 1600 gm. An additional limitation is that only concentrations were measured and not the total amount of circulating protein.[12]

Comparison of the values reported here with those of other investigators is difficult due to differences in chemical methods, size and age of patients and the wide variations in the concentrations of the serum proteins in apparently healthy premature infants. The earlier literature has been covered by Smith[5] and Young et al.[13]

No correlation of levels of total serum protein in the first few days of life with birth weights was found in the authors' data nor those of others,[13–16] despite the significant rise in albumin and globulin in cord blood with increasing length of gestation reported by Rimington and Bickford.[17]

The downward trend of total serum protein concentration within the first 30 days was noted by Rothe-Meyer[15] and Künzer et al.[18] using Kjeldahl determinations and by Smith[14] using a biuret method. Young[13] using a modified Kjeldahl procedure, found this trend only in the smaller infants. McMurray et al.,[19] using Folin's phenol reagent, did not find a decrease in total serum protein concentrations with increasing age.

Due to the differences between the various salting-out procedures and separation by electrophoresis it seems fruitless to attempt comparisons. The earlier electrophoretic analyses of Moore[11] cannot be directly compared with this data because of differences in technic and because he gave no total protein figures. However, expressed in planimeter units, Moore[11] found at one month of age the area for albumin had increased in 2 out of 3 measurements and at 2 months only 1 out of 3 determinations were above the values he had for the first 10 days of life. The present authors' values for albumin, expressed in the same units, reveal a gradual decline during this period. There is no definite trend of the area of beta globulins in either Moore's or this data during the first two months.

The concentrations of gamma globulins in these patients plotted on semilogarithmic paper reveal a fairly linear decline in the values during the first six weeks, although some of the consecutive levels for an individual patient do not follow this pattern. Roughly the concentration of the gamma globulins decreases to one-half its original value in 22 to 24 days. A similar trend in the values for gamma globulin in full-term newborn infants has been presented recently.[20] Thus the rate of decrease in the total gamma globulin fraction in these patients is more rapid than the rate of disappearance found by Barr

et al.[21] for diphtheria antitoxin in newborn infants. Clearly the values for the concentration of the total gamma globulin fraction do not parallel the clinical immunity of infants to all the diseases to which they have transplacental passive immunity.

Summary

Forty-four measurements of the concentrations of total serum protein determined by a Kjeldahl procedure and of albumin, alpha 1, alpha 2, beta and gamma globulins determined electrophoretically in the serum of 27 premature infants ranging in age from 7 hours to 65 days are reported.

Wide variations in all values are evident in individual cases. Certain trends are nevertheless apparent. During the first 5 to 6 weeks there is a gradual decline in the concentrations of total serum protein, albumin and gamma globulins. The alpha and beta globulins show no trend with age in this study.

Except for slightly higher values for alpha 1 globulins in the smaller infants, none of the concentrations could be correlated with the birth weights of the patients.

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References

1. Dancis, J., O'Connell, J. R., and Holt, L. E., Jr., Grid for recording weight of premature infants, J. Pediat. **33**:570, 1948.
2. Hiller, A., Plazin, J., and van Slyke, D. D., Study of conditions for Kjeldahl determination of nitrogen in proteins, J. Biol. Chem. **176**:1401, 1948.
3. Darrow, D. C., and Cary, M. K., Serum albumin and globulin of newborn, premature and normal infants, J. Pediat. **3**:573, 1933.
4. Young, W. F., Hallum, J. L., and McCance, R. A., Secretion of urine by premature infants, Arch. Dis. Child. **16**:243, 1941.
5. Smith, C. A., Physiology of Newborn Infant, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951.
6. Moore, D. H., Roberts, J. B., Costello, M., and Schonberger, T. W., Factors influencing electrophoretic analysis of human serum, J. Biol. Chem. **180**:1147, 1949.
7. Longsworth, L. G., Recent advances in study of proteins by electrophoresis, Chem. Rev. **30**:323, 1942.
8. Longsworth, L. G., Modification of Schlieren method for use in electrophoretic analysis, J. Am. Chem. Soc. **61**:529, 1939.
9. Tiselius, A., and Kabat, E. A., Electrophoretic study of immune sera and purified antibody preparations, J. Exper. Med. **69**:119, 1939.
10. Armstrong, S. H., Jr., Budka, M. J. E., and Morrison, K. C., Preparation and properties of serum and plasma proteins: Quantitative interpretation of electrophoretic Schlieren diagrams of normal human plasma proteins, J. Am. Chem. Soc. **69**:416, 1947.
11. Moore, D. H., duPan, R. M., and Buxton, C. L., Electrophoretic study of maternal, fetal and infant sera, Am. J. Obst. & Gynec. **57**:312, 1949.
12. Metcoff, J., and Stare, F. J., Medical progress: Physiologic and clinical significance of plasma proteins and protein metabolites, New England J. Med. **236**:26, 1947.
13. Young, W. F., and others, Protein requirements of infants: Nutrition of premature infants, Arch. Dis. Child. **25**:31, 1950.
14. Smith, C. A., Phillips, K. G., and Roth, R. O., Effects and fate of human serum albumin administered intravenously and orally to premature infants, J. Clin. Investigation **29**:218, 1950.
15. Rothe-Meyer, A., Serum protein and blood urea in prematures on high protein nutrition, Acta paediat. **38**:551, 1949.

16. Reardon, H. S., and others, Studies of acid-base equilibrium in premature infants, PEDIATRICS 6:753, 1950.
17. Rimington, C., and Bickford, J. A., Pre- and post-natal development of immunity: Serum-albumin and serum-globulin levels in maternal and cord bloods of premature infants, Lancet 1:781, 1947.
18. Künzer, W., Zauner, J., and Zeisel, H., Der Serumeiweissgehalt von Unreifgeburten, Klin. wchnschr. 29:327, 1951.
19. McMurray, L. G., Roe, J. H., and Sweet, L. K., Plasma protein studies on normal newborns and premature infants, Am. J. Dis. Child. 75:265, 1948.
20. Orlandini, T. O., Sass-Kortsak, A., and Ebbs, J. H., Serum Gamma Globulin Levels in Infancy, read at the Annual Meeting of the Society for Pediatric Research, Old Point Comfort, Va., May 1952.
21. Barr, M., Glenny, A. T., and Randall, K. J., Concentration of diphtheria antitoxin in cord blood and rate of loss in babies, Lancet 2:324, 1949.

SPANISH ABSTRACT

Análisis Electroforético de las Proteínas del Suero en Niños Prematuros

En este estudio se hace un análisis de 44 determinaciones de las concentraciones de las proteínas totales del suero determinadas por el método de Kjeldahl y de la albúmina, así como de las globulinas alpha 1, alpha 2, beta y gamma en el suero sanguíneo de 27 prematuros que oscilaban en edad entre 7 horas y 65 días.

Los autores encontraron grandes variaciones en todos los valores de los casos individualmente, sin embargo, ciertas tendencias son aparentes. Efectivamente, se puede apreciar que durante las primeras 5 a 7 semanas la concentración de las proteínas totales albúminas y gamma-globulinas sufren un descenso gradual. La alpha y beta globulinas no mostraron ninguna tendencia con la edad.

Excepción hecha de los valores para las globulinas alpha 2 que fueron ligeramente mayores en los niños mas pequeños, ninguna de las concentraciones pudieron ser correlacionadas con los pesos de nacimiento de los enfermos.

477 First Avenue

LEVEL OF HYALURONIDASE INHIBITOR IN THE SERUM OF PREMATURE INFANTS WITH RETROLENTAL FIBROPLASIA

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AMONG the handicaps with which the premature infant is confronted is its susceptibility to the newly recognized disease, retrolental fibroplasia. Terry[1] first described this syndrome in the premature infant in 1942. It is a disease which appears at about the fourth to sixth week of life, involving primarily the retina of the eye. Initially, there are vascular changes in the retinal vessels, consisting of dilatation of the veins and tortuosity of the arteries. Subsequently, retinal detachment with new blood vessel formation takes place and "scarring which pulls the retina into a disorganized mass behind the lens."[2] The disease may not progress in a regular fashion but may regress at any time. The damage to vision is dependent on the irreversible changes which have occurred prior to regression. One of the first, though by no means consistent, findings in the eyes of a premature baby who will subsequently develop some degree of retrolental fibroplasia is a transient haziness of the vitreous, accompanied by the presence of fine discrete bits of material floating in the vitreous.

Meyer and Palmer[3] in 1934 first demonstrated that the mucopolysaccharide, hyaluronic acid, occurs in bovine vitreous humor and these workers[4] later demonstrated that this substance was also present in the aqueous chamber. While the role of hyaluronic acid in the vitrous is unknown, Meyer[5] has suggested that it is probably concerned with the maintenance of the turgor of the vitreous body.

Inasmuch as the transparency of the cornea and of the vitreous is presumably due to the presence of hyaluronic acid, the author became interested in the possibility that a change in the mucopolysaccharides of the eye may be associated with retrolental fibroplasia. One way in which this could come about would be by a decrease in the substances that inhibit the hyaluronic acid-splitting enzyme normally present in body tissues.

The so-called nonspecific or physiologic inhibitor found in the sera of normal individuals is a nondialyzable and heat-labile substance.[6, 7] While its chemical nature has not been established, Glick and Moore[7] have shown that the inhibitor migrates with albumen in an electrophoretic field. Most workers agree that the inhibiting activity is due neither to an antibody nor to an enzyme reacting specifically with hyaluronidase.[8] The present communication is a brief summary of findings on the level of physiologic inhibitor present in the sera of normal prematures and those infants showing varying stages of retrolental fibroplasia.

MATERIALS AND METHODS

Turbimetric method as described by Epstein and associates[9] was employed with minor modifications. Samples of sera obtained aseptically by heel prick from premature infants were not oxalated, since

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calcium and magnesium have been reported by Baumberger[10] and Freeman[11] as essential for activation of the inhibitor. Prior to use, each sample of serum was diluted 1:10 with 0.15 M saline. Since the inhibitory activity of 0.05 cc. serum was tested in each determination, instead of 0.1 cc. which Epstein used, the volume of each reagent employed in the reaction was accordingly halved. In order to prevent growth of micro-organisms, some of which are know to contain hyaluronidase and others, hyaluronic acid, the buffers and all glassware were autoclaved for 30 min. at 20 lbs. pressure. pH of buffer solutions was checked and adjusted if necessary, prior to use each day. All determinations were carried out in duplicate and the variation between tubes did not exceed 3%. Inhibition of enzyme activity by 0.05 cc. serum is expressed as the per cent reduction in turbidity of a standard solution of hyaluronidase (4.5 turbidity-reducing units) and 0.75 mg. hyaluronic acid employed as substrate. Standard curves for different amounts of enzyme were run simultaneously each time determinations of the inhibitor titer of sera were run.*

Results

The premature infants who comprised this study were babies admitted to the Colorado General Premature Infant Center. These infants were fed a formula consisting of diluted powdered half-skimmed cow's milk with added carbohydrate.[12] Vitamins A, D and C were given daily as supplements to this formula. Samples of serum were obtained late in the afternoon with no particular regard to the time the infant was last given his formula. The eyes of the premature infants were examined soon after birth. Those infants showing no signs of retrolental fibroplasia were checked at two week intervals, while those babies showing the first signs of pathology were examined weekly. Dilatation of the eyes was obtained with a solution containing 1% homatropine and 1% paredrine, followed later by 10% neo-synephrine®. The premature infants were kept quiet during the ophthalmoscopic examination by being allowed to suck on a nipple containing a cotton pledget saturated with 5% glucose.

A study of the level of inhibitor present in 20 premature infants, with and without retrolental fibroplasia, is shown in table 1. Every sample of serum tested was found to contain an inhibitory substance which was completely inactivated on heating at 56°C. for 10 minutes.

It can be seen from table 1 that the levels of inhibitor in serum are not conspicuously dissimilar in normal prematures from those with some degree of active or regressing retrolental fibroplasia. The antihyaluronidase titers ranged from 23 to 71%. A series of four inhibitor determinations was made on the serum of Girl Gar: the initial value of 42% was obtained when the first signs of retrolental fibroplasia were noted at 27 days of age. During the following six weeks, three more studies of the content of inhibitor in the serum of this infant gave the following values: 48, 46 and 38%, respectively. In the case of Girl Sur, who showed no signs of eye pathology at any time, inhibitor titers of 66, 48 and 46%, respectively, were observed (table 1). These data indicate that the level of physiologic inhibitor in the serum of the premature infant cannot be correlated with either the presence or the progress of retrolental fibroplasia.

The mean of the hyaluronidase inhibitor with its standard error was 48.3 $\pm$2.49 in the normal premature infants, while the average mean in the babies showing some degree of retrolental fibroplasia was 42.3 $\pm$2.82 (table 1). It is apparent from the magnitude of the standard error of each of the means that the difference of six between the means is not significant. Where more than one determination of the antihyaluronidase titer was made on the same infant, each value was used in statistical analysis.

* The concentration of stabilized serum was doubled, using a 1:10 dilution instead of 1:20 as described by Epstein.

TABLE 1

HYALURONIDASE INHIBITOR IN SERA OF PREMATURE INFANTS WITH AND WITHOUT RETROLENTAL FIBROPLASIA

Infant	Birth Wt., gm.	Gestational Age, wk.	Wt. and Age when Sera Obtained		Inhibition of Enzyme %	Diagnosis of Eyes
			gm.	days		
Mor, Girl	935	29	1550	58	65	Normal
			1780	65	50	Normal
			2010	73	56	RLF
Fro, Girl	1191	—	1550	25	50	Normal
			2170	44	50	Normal
Sur, Girl	1200	35	1300	15	66	Normal
			1720	25	48	Normal
			1840	28	46	Normal
Gre, Girl	1295	30	1610	27	32	Normal
			1790	32	33	RLF
Tie, Girl	1503	36	1580	15	40	Normal
			1990	37	44	RLF
Aft, Girl	2098	35	2206	15	42	Normal
			2280	19	50	Normal
Luc, Girl	2240	30.5	2760	32	46	Normal
Cau, Boy	1304	31	2700	64	37	Normal
Asn, Boy	1470	—	2070	33	39	Normal
Car, Boy	1673	40	1700	24	71	Normal
			2340	38	55	RLF
Tie, Boy	1871	36	1860	15	37	Normal
Cas, Boy	2041	35	2180	12	52	Normal
VanPel, Girl	1080	29	3050	87	34	RLF
			3460	101	27	RLF
			3630	129	54	RLF
Has, Boy	1330	33	2550	58	27	RLF
			2970	65	51	RLF
Hut, Boy	1389	29	2200	46	37	RLF
Gar, Girl	1090	—	1150	27	42	Suspicious
			1620	51	48	RLF
			2000	59	46	RLF
			2360	69	38	RLF
Roo, Girl	1191	32	1900	50	44	Suspicious
Ell, Girl	1750	37	1810	21	65	Suspicious
Sch, Boy	1031	—	1475	37	50	Suspicious
Ell, Boy	1610	37	1720	22	65	Suspicious

No demonstrable trend was apparent when the level of inhibitor in both boy and girl premature infants, with and without retrolental fibroplasia, was plotted against body weight.

In addition to the above series of 20 premature infants, the inhibitory titer of four prematures was studied within the first two weeks of life. Like the older prematures, the serum obtained from these babies exhibited an inhibitory effect on hyaluronidase. However, in contrast to the prematures, 2 weeks of age or older, the inhibition was not due solely to the heat labile factor, for a significant degree of inactivation was obtained even after the serum had been heated. Both types of inhibitory substances were also found to be

present in the blood of full term infants studied during the first two weeks after birth. It was noted that the serum obtained from both the "young" premature and the "young" full term baby (1 to 14 days of age) was deeply pigmented. It may be recalled that Wattenberg and Glick[13] have shown that certain hemoglobin derivatives inhibit the enzyme, hyaluronidase. It seemed likely that samples of pigmented serum contained these heat stable substances. The serum of premature infants 2 weeks of age or older was not pigmented nor, as already indicated, did it contain heat stable inhibitors.

Summary

The serum of the premature infant contains material which inhibits bovine hyaluronidase. This inhibitor was found to be present to about the same degree in infants with and without retrolental fibroplasia and appeared to be unrelated to the severity of the disease.

The level of the physiologic inhibitor of hyaluronidase found in the blood of the premature and full term infant is approximately of the same order of magnitude.

Acknowledgment

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References

1. Terry, T. L., Fibroplastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely: Studies in development and regression of hyaloid artery and tunica vasculosa lentis, Am. J. Ophth. **25**:1409, 1942.
2. Report of the Second M & R Pediatric Research Conference, Columbus, Ohio, M & R Laboratories, 1951, p. 59.
3. Meyer, K., and Palmer, J. W., Polysaccharide of vitreous humor, J. Biol. Chem. **107**:629, 1934.
4. Meyer, K., and Palmer, J. W., On nature of ocular fluids, Am. J. Ophth. **19**:859, 1936.
5. Meyer, K., Physiological significance of hyaluronic acid and hyaluronidase, Physiol. Rev. **27**:335, 1947.
6. Dorfman, A., Ott, M. L., and Whitney, R., Hyaluronidase inhibitor of human blood, J. Biol. Chem. **174**:621, 1948.
7. Glick, D., and Moore, D. H. Hyaluronidase inhibitor in electrophoretically separated fractions of human serum, Arch. Biochem. **19**:173, 1948.
8. Dorfman, A., Action of serum on hyaluronidase, Ann. New York Acad. Sc. **52**:1098, 1950.
9. Epstein, N., Lubchez, R. L., DeGara, P. F., and Wilson, May G., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever, Pediatrics **4**:569, 1949.
10. Baumberger, J. P., and Fried, N., Magnesium as activator of antinvasin, J. Biol. Chem. **172**:348, 1948.
11. Freeman, M. E., Whitney, R., and Dorfman, A., Magnesium and hyaluronidase inhibitor of blood serum, Proc. Soc. Exper. Biol. & Med. **70**:524, 1949.
12. Gordon, H. H., Levine, S. Z., and McNamara, H., Feeding of premature infants: Comparison of human and cow's milk, Am. J. Dis. Child. **73**:442, 1947.
13. Wattenberg, L. W., and Glick, D., Mucolytic enzyme systems. VII. Effect of tissue extracts and body fluids, certain steroids and hemoglobin derivatives on hyaluronidase, J. Biol. Chem. **179**:1213, 1949.

Spanish Abstract

El Nivel de la Substancia Inhibidora de la Hialuronidasa en el Suero de Niños Prematuros con Fibroplasia Retrolental

La fibroplasia retrolental es un síndrome descrito por primera vez por Terry, en 1942, de localización inicial en la retina del ojo y que se presenta entre la cuarta y la sexta semana de la

vida en los niños prematuros. Se inicia con alteraciones vasculares de la retina caracterizados por dilatación de las venas y tortuosidadede las arterias; subsecuentemente se presenta desprendimiento de la retina con formación de nuevos vasos sanguíneos y cicatrización que hace tracción de la retina hacia atrás del cristalino apareciendo como una masa informe. La enfermedad puede no progresar uniformemente pues puede regresar en cualquier momento y el daño producido en la visión depende de los cambios irreversibles ocurridos.

Uno de los primeros hallazgos, aunque no infalible, que se encuentran en los ojos de un prematuro que posteriormente presente cierto grado de fibroplasia retrolental, es una opacidad transitoria del humor vítreo acompañada de la presencia de finos fragmentos de substancia que flotan en su interior.

Se ha demostrado que el ácido hialurónico, que es un mucopolisacárido, existe en el humor vítreo y en la cámara acuosa y aunque su papel en el vítreo es desconocido se ha sugerido que probablemente tiene alguna intervención en el mantenimiento de su turgencia.

Como por otra parte se presume que la transparencia de la cornea y del vítreo son debidas al ácido hialurónico el autor le pareció interesante investigar la posibilidad de que un cambio en los mucopolisacáridos del ojo pudiera estar asociado con la fibroplasia retrolental y decidió comprobar si existía una disminución de las substancias que inhiben la acción de la enzima que hace la demolición del ácido hialurónico y que se encuentra normalmente en los tejidos del organismo. Poco se sabe acerca de dicha substancia llamada inhibidor fisiológico o no específico que se encuentra en el suero de individuos normales; no es dializable, es termolabil, emigra con la albúmina en el campo electroforéfico y parece que su actividad inhibidora no es debida ni a una reacción de anticuerpo o enzimática específicamente con la hialuronidasa. Con estos antecedentes se realizó la determinación del nivel del inhibidor fisiológico en el suero de 20 prematuros unos normales y otros con fibroplasia retrolental en diferentes estadíos.

El estudio demuestra que la substancia inhibidora de la hialuronidasa se encuentra en el mismo grado en el suero de los niños con o sin fibroplasia retrolental y parece no tener relación alguna con la severidad de la enfermedad, y los niveles tanto en los prematuros como en niños a termino son aproximadamente de la misma magnitud.

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BIRTH AND MORTALITY RATES AMONG SLAVE INFANTS ON SOUTHERN PLANTATIONS

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THERE seems to be no end of writings about the Ante-bellum South but one of the most neglected fields has been the health of the slaves. Recently a monograph appeared dealing with this subject and since there are no better criteria in judging health standards than a study of infant birth and mortality rates, a further interpretation of the data presented in this monograph with some additional facts is herewith presented.[1] There was nothing the planter was more interested in than the increase of his slaves through the birth and rearing of children, and within the bounds of medical knowledge of the period, he took the time and effort to promote conditions that were conducive to the rearing of large families.

The first care of the planter was the prenatal care of the mother. Rules were drawn up by the planter and overseers were instructed in the care of the expectant mother. Crude as this care was in comparison to our knowledge today it was still far superior to anything the Negro had known in Africa, and it compared favorably with the medical knowledge of the ante-bellum period. As soon as the mother reported her condition she was assigned lighter tasks.[2] On confinement she was sent to the lying-in room of the plantation hospital or, if the plantation was large enough, to a separate hospital maintained for such cases. Throughout rural America confinement cases were usually handled by midwives or "grannies" as they were sometimes known. A Negro woman would serve as midwife for the plantation, serving both white and black. Such was not always the case, however. Many records are available showing that physicians were frequently employed in confinement cases.[3] When the occasion demanded, cesarean sections were performed. Dr. Robert P. Harris of Philadelphia, in investigating the number of cesarean sections in the United States, reported 15 cases performed upon Negro slave women in Louisiana, resulting in the saving of both mother and child in a majority of cases. Strange as it may seem one of these sections was performed by a plantation midwife.[4]

The planters were just as careful in the postnatal care of the mothers as they were in the prenatal care. The general rules on all plantations were for the mother to remain in the house or hospital four weeks after the birth of her child and longer if she was not well. She was then assigned light tasks for two weeks or more if necessary. A check of the planters' records indicates that as a whole the planters adhered to this rule.[5]

The care of the infant occupied the attention of both the owner and overseer. The economic consideration cannot be overlooked as an important motive for the concern of the planter. As one planter expressed it: "Children of course, must be fed and attended to as their wants require: they are not likely to be neglected, as they pay a good interest upon the amount of care and expense bestowed upon them."[6] The vexing problem of feeding was no problem to the midwife. She realized that nature's food was the best and

From the Library, Louisiana State University School of Medicine, New Orleans.
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let it go at that. That was probably the biggest single factor in the small percentage of infant deaths during the first month as compared to the remainder of the year. As soon as the mothers returned to the field the babies were left in charge of a nurse. Four times a day, as a rule, the mothers returned to the nursery for half hour periods to nurse their babies. The nurse was particularly instructed to see that the infants were not nursed while the mothers were overheated. To safeguard against this the mothers were required to rest for 15 minutes before nursing. The supervision of the infants required constant attention, since many slave mothers could not be trusted to care for their babies. The administering of medicines usually had to be attended to by the planter's wife or the nurse.

The infants suffered all the afflictions and diseases common at that time. Many mothers smothered their babies by rolling on them while sleeping. One of the common causes of infant deaths was tetanus known as trismus infantum, a result of the improper dressing of the umbilicus. Cholera infantum, diarrhea or dysentery was listed as the cause of many an infant death. Infants suffered all the other ailments common to childhood. Measles, whooping cough, croup, sore throat, pneumonia, mumps, thrush, colic, colds, fits, convulsions are all listed in the planters' books, so that one can sympathize with one planter when he exclaimed: "I am at a loss what to do for my little Negro children. They die at 3 and 6 months without their diseases ever yielding to treatment."[7]

The food issued children was specified in most planter's rules. Usually the amount of ration was in proportion to that issued a prime field hand. One planter stated that children were to have hominy, milk and cold corn bread for breakfast; vegetable soup and dumplings or bread for dinner; and cold bread or potatoes were to be kept on hand for demands between meals. Molasses were provided once or twice a week, and each child was given a pan and spoon to be left in charge of the nurse.[8]

Clothes were a minor problem in the Lower South. The small children were usually dressed in a single garment. The material distributed as a rule included osnaburgs and shirting in summer, and woolen and shirting in winter. Calico was issued on some plantations. The amount depended on the size of the child. One planter had an unusual method of determining the amount of cloth to be issued. To each child he gave twice its length in cloth.[9] Shoes were distributed to the children during the winter months. During summer the custom of going barefooted prevailed. Blankets were provided as needed. Customs varied from plantation to plantation, but as a whole the children were amply provided from the standpoint of health.

Since the mothers were too valuable as field hands to be permitted to remain home after they were well enough to return to the fields, the responsibility of caring for the infants was the duty of the "children's nurse." The babies were left at the nursery when the mothers left for the fields in the morning. The organization of the nursery depended a great deal upon the size of the plantation. On small estates the plantation cook took care of the few children on the plantation. On large estates it became necessary to assign a special nurse to care for the sick and the children. Although as a rule the children's nurse was an old or invalid Negro, it cannot be said that she did not have some qualifications for her job as attested to by the statements of many planters. The nursery might adjoin the hospital or plantation kitchen depending upon the division of duties of the nurse, or it might adjoin the lying-in room or hospital so the mothers could be next to their infants. The size of the nursery depended upon the size of the plantation. An ordinary cabin served the purpose of most plantations while on large estates the nursery was considerably larger.

Although the care of infants may seem primitive in comparison to present standards, a comparison to the conditions of that time gives a different impression as to what was accomplished by the planter in caring for his slave infants. Infant mortality for the country as a whole was high. Very little reliability can be placed on the early census reports. Still when the 1850 census reports infant mortality per 1000 births as 105 for Louisiana and 121.5 for Massachusetts the impression is that infant mortality was very high.[10] Particularly is this true when it is realized that infant mortality rates in 1948 are 32.0 per 1000 live births.[11]

In evaluating health conditions among slave infants, data relating to infant births were compiled. From the plantation records of 12 plantations scattered throughout the South the birth rates were computed. Their rates ranged from 23.2 in 1840 to 116.6 in 1834 with a median of 54.2. These rates are based on a slave population of 8,274 and 451 live births.[12] In 1948 the birth rate per 1000 for the registration area of the United States was 24.2.[13] These rates are not significant in showing any trend, but they are indicative of the high birth rate among slaves.

One of the most significant records in evaluating slave health is the infant mortality rate. These figures were assembled from 14 plantations from the States of Georgia, Louisiana, Mississippi, South Carolina and Virginia. The period covered extends from 1817 through 1861, and in most cases represents a fairly long period of time for each plantation. The infant mortality rate per 1000 for this group based on 1,114 live births and 170 infant deaths is 152.6.[12] Although this rate is high compared to the rate today (32.0 per 1000) it is not unduly high for the ante-bellum period. As late as 1916 the rate for the registration area of the United States was 101.0 for all races.[14] In 1915 Massachusetts, New York and Pennsylvania reported infant mortality rates for Negroes as high as 163, 192 and 185.[15] The rates for some of the Southern States in 1918 were Kentucky, 192; North Carolina, 140; and Virginia, 142.[15] For the registration area of the United States the infant mortality rate of Negroes was 99.5 in 1930 and 74.1 in 1941.[16] By comparison with these figures a rate of 152.6 is not excessive for the ante-bellum period.

Further study of infant mortality figures for one month after birth (neonatal) reveals some interesting probabilities. For the registration area of the United States in 1942 the distribution of neonatal deaths was 64% of total infant mortality.[17] This percentage was 47.1 in New Jersey in 1898, one of the earliest states to report neonatal deaths.[18] A compilation of slave infant deaths was made from plantations which reported dates of births and deaths, thus enabling calculation of deaths for one month after birth. These figures were: births, 784; infant deaths, 167; neonatal deaths, 60, making the distribution of neonatal deaths 35.9% of total infant mortality.[19]

Due to the advances made in treating diarrheal and respiratory infections the mortality rate for infants for the 2 to 12 month period after birth has dropped from 58.1 in 1915 to 9.8 in 1948, thereby causing a drop in percentage of infant deaths (deaths under one year) for the 2 to 12 month period.[20] In comparison the neonatal rate has only dropped from 44.4 to 22.2 for the same years.[21] This has resulted in an increase in the percentage of deaths for the neonatal period while decreasing the percentage for the 2 to 12 month period. An advance release of the Federal Security Agency calls attention to the comparatively high mortality rate for babies under one month and states that, although infant mortality has been cut by more than two-thirds in the last 30 years, the savings are chiefly among full term babies after the first month.[22]

On the plantations herewith studied conditions were reversed. For the neonatal period the percentage of slave infant mortality was 35.9 of total infant mortality. This indicates that the pre- and postnatal care of the slave mothers and the care of the neonatal infants was very good for that period even though it appears crude in comparison to present-day knowledge. After the first month the lack of knowledge of infant care resulted in high mortality rates from diarrheal and respiratory infections.

In conclusion it may be said that the records of infant births and mortalities compiled from planters' records of from 12 to 14 plantations throughout the South indicate that birth rates were much higher than the rates today; that infant mortality rates compared favorably with conditions for that period; and that the neonatal care of slave infants was very good for these ante-bellum plantations.

References

1. Postell, W. D., Health of Slaves on Southern Plantations, Baton Rouge, 1951.
2. Phanor Prudhomme, Account Book, Aug. 20, 1860, in the Phanor Prudhomme Records, Southern Historical Collection, University of North Carolina. Magnolia Plantation Journal, Oct. 20, 1856, in the Henry Clay Warmoth Papers, Southern Historical Collection, University of North Carolina. Eli J. Capell, Plantation Diary, III, Feb. 26, 1849; IX, July 31, Aug. 1, 6, 7, 1855, in the Capell Diaries, Department of Archives, Louisiana State University.
3. George W. Graves, Physicians Fee Book, Nov. 11, 1850; Aug. 8, 1848, in the George W. Graves Collection, Southern Historical Collection, North Carolina. William P. Graham, Physicians and Druggist Ledger, Feb. 12, 1828, Aug. 17, 1830, "Account of Joshua Willis"; Nov. 27, 1827, Nov. 6, 1828, "Account of William F. Walker"; May 30, 1832, "Account of James C. Branch," in the William P. Graham Collection, Southern Historical Collection, North Carolina. Robert H. Ryland, I, June 6, 1854, "Account of Mr. Cabel," in the Robert H. Ryland Collection, Department of Archives, Louisiana State University.
4. Harris, R. P., Record of Caesarean operations that have been performed in State of Louisiana during present century, New Orleans M. & S.J. **6**:933, 1879.
5. Postell,[1] chap. 7.
6. Collins, R., Management of slaves, De Bow's Review, **17**:423, 1854.
7. Newstead Plantation Diary, Aug. 7, 1858, Southern Historical Collection, North Carolina. (microfilm)
8. Phillips, U. B., American Negro Slavery, New York, 1918, p. 266.
9. Manigault, L., Plantation Book, Dec. 9, 1841, "Negroes at Gowrie, Savannah River and clothes given them," in the Manigault Plantation Records, Southern Historical Collection, North Carolina.
10. U. S. Bureau of the Census, Seventh Census of the United States, Washington, 1850.
11. U. S. National Office of Vital Statistics, Vital Statistics of the United States (1948), I, 6.
12. Postell,[1] chap. 9.
13. U. S. National Office of Vital Statistics, Vital Statistics of the United States (1948), I, 3.
14. U. S. Bureau of the Census, Statistical Abstract of the United States (1946), 70.
15. U. S. Children's Bureau, table IM-3.
16. U. S. Children's Bureau, chart no. IM 41-10.
17. U. S. Children's Bureau, Births, Infant Mortality, Maternal Mortality in 1942 (Washington, 1945), 7 A.
18. New Jersey, Board of Health Twenty-second Annual Report, 1898, 488.
19. Peter Gaillard, Plantation Book, in the Peter Gaillard Papers, South Carolina Historical Society Library. Joseph Kleinpeter, A memorandum of the births of Negroes Children on Variety Plantation, Plaquemine, La. In possession of Mrs. Ludovic Patin, New Roads, La. Thomas W. Butler Papers, Department of Archives, Louisiana State University. Moses and St. John Liddell Collection, Department of Archives, Louisiana State University.
20. U. S. Children's Bureau, Changes, in Infant, Childhood, and Maternal Mortality, over the decade 1939-1948, Statistical Series Number 6, chart I-B.
21. Ibid., chart I-A.
22. Federal Security Agency, Advance Release, FSA-743, Feb. 23, 1950, 2.

SPANISH ABSTRACT

Coeficientes de Natalidad y Mortalidad entre los-Lactantes Esclavos de las Plantaciones del Sur

El estudio del autor del artículo pone de manifiesto que los coeficientes de natalidad en los esclavos de las plantaciones del Sur de los Estados Unidos de Norte-américa eran mayor que los actuales. La atención prenatal y postnatal de las madres esclavas y la atención del recién nacido era muy buena para dicha época aún cuando aparezca inadecuada comparada con respecto a nuestros conocimientos actuales. Igualmente los coeficientes de mortalidad pueden ser comparados favorablemente con los actuales de acuerdo con el adelanto de esos días.

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ADRENOCORTICOTROPHIC HORMONE (ACTH) THERAPY OF THE NEPHROTIC SYNDROME IN CHILDREN

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ADMINISTRATION of adrenocorticotrophic hormone (ACTH) commonly results in diuresis and at least temporary remission of the nephrotic syndrome.[1-6]

This report will describe some of the clinical and physiologic responses to this form of therapy as observed in 56 courses administered to 45 patients with the nephrotic syndrome from July 1949 to April 1951. It will indicate that although this type of therapy usually is not curative it appears to be the treatment of choice at present, since a successful diuretic response is associated with improved renal function and may interrupt the progression of the disease. Possible complications, particularly those of biochemical or infectious nature, require constant vigilance during and immediately after use of the hormone, and hence will be discussed in considerable detail.

MATERIALS AND METHODS

Patients selected for treatment had classical manifestations of the nephrotic syndrome: insidious onset of typically massive edema associated with oliguria, marked proteinuria, hypoproteinemia and hyperlipemia. Transient hypertension had been noted in some. Azotemia, hematuria and moderately reduced renal function were occasionally present but were not considered in the selection of patients for therapy, since there is evidence suggesting that the nephrotic syndrome is a form of nephritis, and clinical differentiation of "true nephrosis" is arbitrary and probably not valid.[7] Hypertension, recent infection, marked deviations of serum electrolyte pattern, or uremia were considered contraindications to therapy. The shortest duration of the disease prior to treatment was 2 wk., the longest 51 mo., with a median of 5 mo. The youngest patient was 1-9/12 yr. of age when therapy was initiated; the oldest, 11-9/12; the median age of the group, 3-7/12 yr. All patients were hospitalized on an average of from 21 to 28 days.

General management included bed rest, careful observation for evidence of infection, particularly of the skin and upper respiratory tract, blood pressure readings with an appropriate-sized cuff at least twice daily, and daily nude weights before breakfast on a tared scale. An attempt was made to measure fluid intake and output in all patients, but assessment of the latter was frequently impossible in incontinent, edematous, young patients. Desirable fluid intake was estimated as an amount equivalent to approximate urine volume plus the additional fluid necessary to satisfy gastrointestinal and insensible water loss. The latter was considered to be approximately 400 cc./sq.m./24 hr.

The prescribed diet varied from "salt-free" (less than 10 mM Na+, 0.03 to 0.20 gm. NaCl/day) to a ward diet without added salt (up to 90 mM Na+, 3 to 5 gm. NaCl/day). In most instances, appetite was capricious and the total prescribed diet was seldom completely consumed. Antibiotic therapy, usually with aureomycin or another indicated agent, was continued throughout hospitalization in slightly less than full therapeutic dosage. Aureomycin, for example, was given in divided doses totaling 30 to 50 mg./kg./24 hr. After preliminary experience, a dosage schedule of 150 to 200 mg.

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The ACTH used in the initial phases of this study was supplied by the Armour Laboratories, Armour and Company, through the courtesy of Dr. John R. Mote.

TABLE 1

PATIENT DATA

Patient				Therapy with ACTH				Results				
Pt.	Sex	Age (yr.)	Duration Disease (mo.)	Course No.	Date	Dosage mg./D	Dosage Days	Wt., Kg. Before	Wt., Kg. After	Day Onset Diuresis*	Clinical Remission (mo.)	Complications**
Group I—Courses with Diuresis												
RDB	M	2-0/12	6	2	10/4–8/49	75	3	19.1	13.4	+2	4	c
						95	2					
		2-5/12	11	4	3/14–26/50	100	13	19.3	12.6	7	4.5	
		2-11/12	17	5	8/24–9/6/50	100	6					
						110, 120, 130	1 each					
						140	5	16.8	15.3	+1	2	
GBn	M	1-10/12	3	1	12/9–18/49	80	10	17.6	11.7	10	0.5	
SS	F	4-11/12	19	1	1/12–22/50	100	11	19.3	17.1	+5[1]	18***	a
SJ	F	4-8/12	3	1	3/28–4/6/50	100	10	23.5	20.8	+1	7	c
		5-4/12	11	2	12/1–10/50	125	10	29.7	21.8	8	4.5	
JF	M	2-8/12	14	2	9/18–27/50	100	5					
						125	5	15.1	11.3	+1	10***	b
JMa	M	3-0/12	4	1	5/30–6/8/50	100	10	24.8	15.1	8	6	c
CP	F	1-9/12	5	1	6/8–19/50	75	5	10.4	8.8	8	12***	
						80	7					
RDC	M	3-11/12	14	1[2]	6/27–7/6/50	100	10	14.5[3]	15.1	+2	2.5	ax
CH	M	4-0/12	11	1	6/30–7/10/50	100	11	22.4	14.9	11	1.5[4]	ax, c
HS	M	4-3/12	14	1	7/1–10/50	100	10	19.2	15.1	7	12***	ax, c
MK	M	4-0/12	6	1	7/15–24/50	100	10	18.2[5]	17.9	+1	6	ax
RP	M	4-2/12	29	1	7/18–25/50	100	8	18.3	16.5[6]	+6	12***	a
MP	F	3-11/12	8	1	7/19–28/50	100	10	19.8	17.2	+2	1.5	ax, b, c
		4-5/12	14	2	1/23–2/1/51	100	10	24.8	16.4	8	6***	
GR	M	4-2/12	3	1	8/12–21/50	100	10	18.3	14.9	9	?	c
FR	M	5-10/12	5	1	8/18–27/50	100	10	25.7	17.1	10	11***	
GM	M	2-11/12	0.5	1	8/19–28/50	100	10	20.1	14.0	8	11***	b
PH	M	1-11/12	0.8	1	9/22–10/1/50	100	10	14.2	11.3	+1	5.5	b
SM	M	2-3/12	9	1	9/25–10/5/50	100	10	14.7	10.2	10	1	
JR	M	2-7/12	11	1	10/9–17/50	100	8.5	15.2	11.9	8	0.5[7]	ax, b, d, e
RD	M	3-1/12	4	1	10/11–20/50	125	10	19.9	13.4	+2	0.75	
DF	F	3-7/12	3	1	10/17–26/50	125	10	20.7	14.6	9	4	
JG	M	2-1/12	0.8	1	10/28–11/6/50	100	10	16.5	12.2	6	4.5	b
JDy	F	8-2/12	51	1	10/30–11/9/50	125	10	41.1	30.7	9	8***	
TB	M	7-1/12	5	1	11/2–11/50	125	10	28.9	20.4	8	0.5	b
SW	F	4-3/12	2	1	11/7–18/50	100	5	18.9	15.0	11	3	b ? e
						0	2					
						100	5					
RI	M	7-0/12	51	1	11/19–28/50	125	6	27.6	24.2	8	8***	c
						150	4					
MDP	M	10-2/12	6	1	11/18–25/50	125	8	33.2	25.4	+4	0.5	d
JMy	M	3-6/12	6	1	1/25–2/3/51	100	10	16.9	13.2	9	5***	ax, c
RL	M	2-11/12	3	1	1/29–2/5/51	100	8	14.2	13.1	+2	2.5	e
GBd	M	7-5/12	19	1	2/10–19/51	125	5	22.9	20.8	7	5***	
						100	5					
CW	M	2-0/12	2	1	2/23–3/5/51	40[8]	11	15.0	10.9	9	2	a
DR	F	2-0/12	5	1	3/2–12/51	40[8]	4	16.4	11.0	10	3***	a, ax
						80[8]	3					
						100[8]	4					
SK	M	2-9/12	10	1[9]	3/19–28/51	100[8]	10	20.6	15.9	+2	0.5[7]	ax, c
AS	F	6-2/12	1	1	3/19–28/51	120	10	24.0	19.1	+1	3***	b
Group IIA—Courses of 8 Days' Duration with Slight or No Diuresis												
RDB	M	2-1/12	7	3[10]	10/28–11/5/49	30	1	13.3	13.1	—	3.5	
						40	3					
						50	1					
						80	4					
GBn	M	2-5/12	10	2	6/27–7/6/50	100	10	21.8	20.6	—	—	a

TABLE 1 (*Continued*)

Patient				Therapy with ACTH				Results				
Pt.	Sex	Age (yr.)	Duration Disease (mo.)	Course No.	Date	Dosage mg./D	Dosage Days	Wt., Kg. Before	Wt., Kg. After	Day Onset Diuresis*	Clinical Remission (mo.)	Complications**
JF	M	2-4/12	10	1	5/20–29/50	100	10	12.0	11.1	—	—	a
JK	M	1-11/12	6	1	6/13–22/50	80	10	11.7	10.6	—	—	ax
		2-6/12	13	2	1/23–30/51	80	7	14.9	10.8[11]	—	—	a, e
						60	1					
TW	M	3-1/12	11	1	7/10–19/50	100	10	19.2	20.6	—	—	b, d, died
HM	M	3-10/12	8	1	7/18–25/50	100	8	19.1	22.1	—	—	a
CS	F	4-2/12	11	1	8/26–9/2/50	100	8	20.0	16.4[12]			b, d, e, died
CZ	F	2-5/12	6	1[13]	10/3–12/50	100	10	15.8	14.3	—	—	a, b, c, e, died
Group IIB—Courses of Less Than 8 Days' Duration; No Diuresis												
TR	M	2-1/12	3	1	7/18–23/49	20	3	15.3	16.0	—	—***	ax
						40	3					
RdB	M	2-0/12	5.5	1	9/24–28/49	20	1	20.3	18.6[14]	—	—	
						30	4					
RG	M	3-10/12	15	1	11/14–18/49	80	5	15.6	15.2	—	—	ax, b
			15	2	11/25–29/49	80	5	15.3	15.3			ax, a,[15] b
JDm	F	11-9/12	3	1	5/31–6/5/50	120	6	40.7	39.8	—	—	b, d[16]
RD	M	3-4/12	7	2	1/17–19/51	100	2	19.1	15.9	—	—	ax, a, died
RM	M	2-8/12	5	1	11/6-10/50	100	5	21.1	19.9	—	—	a, b, d, e
LJ	F	3-5/12	1	1	11/14–17/50	100	4	21.7		—	—	[17]
MB	F	8-1/12	4	1	3/12–17/51	140[8]	3	43.0	40.7[18]	—	—***[19]	
						120[8]	3					

*† Preceding number refers to day after cessation of therapy. Without prefixed +, number refers to day of therapy on which diuresis began.

** Complications denoted by letters are a = Paracentesis. Before ACTH administered = ax
b = Hyponatremia
c = Hypokaliemia
d = Hypertension
e = Infection

*** Clinical remission at time of writing.

[1] Nondraining paracentesis performed 24 hr. before onset of diuresis.

[2] Six previous courses of ACTH (Sept. 1949–Feb. 1950) had been administered elsewhere with 2 of these resulting in excellent diureses.

[3] Weight resulted from paracentesis, performed of necessity shortly after admission when weight was 20.3 kg. Drainage had ceased before initiation of ACTH therapy. Weight after 10 days of therapy was 17.3 kg. Marked increase in appetite occurred.

[4] Temporary recurrence of edema followed by spontaneous diuresis. Has remained edema-free for approximately 8 mo.; but slight hypertension, azotemia, acidosis, proteinuria and hematuria persist.

[5] Weight 24 hr. after paracentesis. No further drainage from wound. After 10 days of ACTH therapy, weight = 22.94 kg.

[6] Diuresis began on 6th post-ACTH day and continued at home. Edema-free state reached after discharge, hence last weight doesn't reflect degree of diuresis. Massive recurrent ascites necessitated paracentesis on this child at beginning, and again 4 days after completion of therapy. There was no significant drainage from wound after first few hours.

[7] Recurrent edema associated with respiratory infection; spontaneous diuresis occurred. Edema-free and in clinical remission since.

[8] Long-acting ACTH (ACTH in oil) supplied by Dr. J. R. Mote of Armour & Co. A single injection was given each 24 hr.

[9] This patient stated to have received a course of nitrogen mustard at home 6 wk. earlier. Only apparent result was typical bone marrow change and anemia. Had received 1 course of ACTH in low dosage for 10+ days elsewhere 4 mo. before admission to Children's Hospital. No response at that time.

[10] It will be noted that this was early in authors' experience with ACTH therapy. Although essentially edema-free following ACTH-induced diuresis some 2 wk. earlier a third course was given this patient because of persistence of slight facial puffiness and continued proteinuria.

[11] Paracentesis performed on the 7th post-ACTH day.

[12] Infection, hypertension, hypotonicity culminated in convulsion on the 4th post-ACTH day. Considerable intravenous therapy with concentrated NaCl, KCl, $NaHCO_3$, and Ca gluc., as well as mag. sulfate were employed. Diuresis began about this time. Because of IV therapy patient couldn't be weighed, nor factors initiating diuresis be evaluated. 16.4 kg. represents weight approximately 1 wk. later. Coma persisted. This patient died 42 days after convulsion.

[13] A previous, unsuccessful course of ACTH had been administered elsewhere.

[14] Slight diuresis occurred in first few days following therapy with immediate recurrence of edema.

[15] Thoracentesis was also performed for large pleural effusion.

[16] Azotemia (NPN 148 mg./100 cc.) and hyponatremia accompanied hypertension and were reason for cessation of therapy. Convulsions with hypertensive encephalopathy occurred 16 days later.

[17] ACTH therapy stopped because of psychosis and melena. Barium enema normal. On aureomycin. Subsequent aureomycin in large doses did not result in melena or other untoward manifestations.

[18] Weight loss due to oozing from skin striae resulting from extreme anasarca.

[19] Subsequent excellent cortisone response approximately 1 mo. after ACTH therapy. Clinical remission has persisted.

ACTH*/sq.m./24 hr. injected intramuscularly in 4 equally divided doses every 6 hr.,† was employed,‡ and continued for 10 days whenever possible.

Surface area was computed from a standard nomogram constructed from DuBois' formula,§ using standing height and presumed nonedematous weight, based either on parents' estimate or on appropriate weight for patient's height in a standard percentile chart.

Observations according to a regular schedule were carried out in most patients with only occasional exceptions. These included, in addition to the usual clinical observations such as temperature, weight and blood pressure, hematologic and blood chemical studies 5 days before the start of therapy, just before its institution, on the 5th and 10th days of treatment, and 5 days after its completion. Certain determinations were made more frequently during the course of treatment and renal functions were estimated the day before instituting treatment and 5 days after its cessation. In most instances, chemical determinations were carried out by the clinical laboratory staff of the hospital according to accepted standard technics. Serum proteins were determined by a micro-Kjeldahl technic, Na and K by flame photometry.[8]

Twelve hour semiquantitative urinalyses were performed on most patients in this series before, during, and after ACTH therapy according to a modified Addis technic.[9] Urinary protein excretion was estimated by standardized alcoholic phosphotungstic-acid precipitation.[10]

Results and Comments

A. Clinical Responses

1. Diuresis: Pertinent clinical features for each patient are summarized in table 1. As edema is the most striking and distressing feature of the disease, diuresis was chosen as the most obvious endpoint of successful response to ACTH therapy although loss of edema through diuresis is not synonymous with cure of the primary renal disease. The series has been divided into 2 major groups:

I. Courses with complete diuresis

II. Courses with slight or no diuresis

(a) Courses of 8 or more days' duration.

(b) Courses of less than 8 days' duration.

The separation of Groups IIA and IIB is arbitrary, but based on the observations recorded in chart 1.

Diuresis, characterized by frequency and increased urine volume with complete loss of edema, occurred in 38 (68%) of the total of 56 courses, or 38 (81%) of 47 full courses of 8 or more days' duration (Groups I and IIA).**

In Group I, diuresis was usually characterized by slight (>0.2 kg.) daily weight loss for 1 to 3 days followed by an abrupt, profuse diuresis with loss of 1 to 3 kg./day for 3 to 5 days, or until the patient became almost edema-free. Continued but less profuse diuresis resulted in complete loss of edema usually within a total of 7 days after the diuresis had begun. With a 10 day therapeutic course diuresis usually began within the 48 hr. period just before or after cessation of therapy—i.e., from the 8th to 12th day (chart 2). Of the 38 patients undergoing diuresis, in 23, diuresis began during the course of treatment; in 15, after therapy had ceased.

In general, personality and behavior changes during treatment usually were similar to those

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* Armour Standard LA-1A.

† In 4 patients Adactar (Armour), a long-acting preparation containing ACTH in oil, kindly supplied by Dr. J. R. Mote of Armour & Co., was injected in a single dose at 24° intervals. A well sustained eosinophil response was obtained. No untoward systemic or local effects related to the injection were noted.

‡ Because of the tendency of puncture wounds in these patients to leak and diminished absorption with extreme edema, intramuscular injections were usually administered in the deltoid region rather than in the anterior thigh or buttocks.

§ $SA = W^{0.425} \times H^{0.725} \times 71.84$.

** Since this report was prepared for publication, an additional 29 courses of ACTH therapy have been administered to 26 patients using the same 10 day schedule. Diuresis was induced in 85% of courses and 81% of patients. Severe complications were observed less frequently.

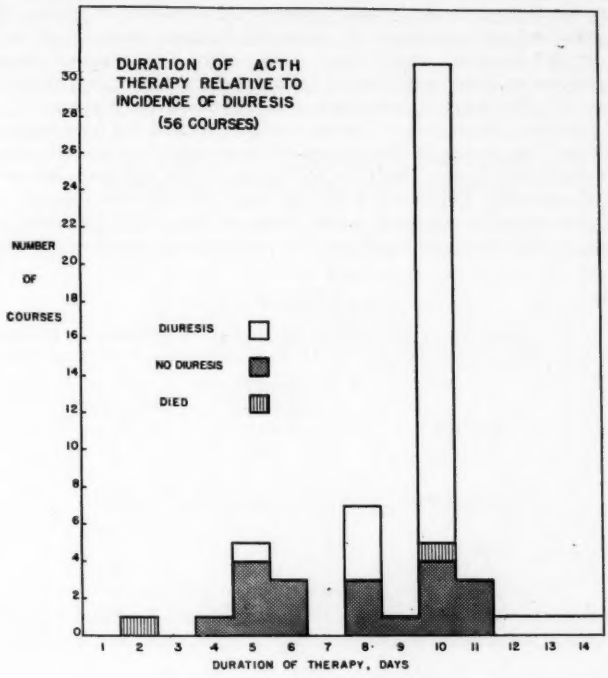

CHART 1

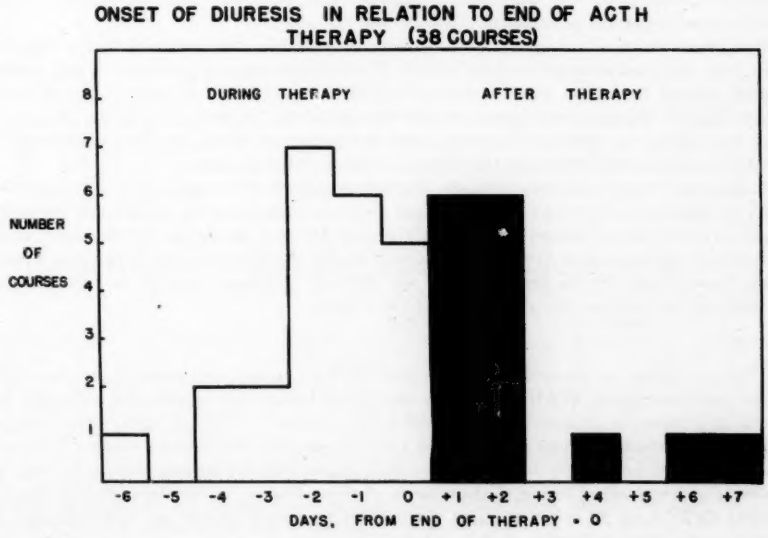
ONSET OF DIURESIS IN RELATION TO END OF ACTH THERAPY (38 COURSES)
DURING THERAPY
AFTER THERAPY
NUMBER OF COURSES
DAYS, FROM END OF THERAPY = 0

CHART 2

accompanying increasing edema in nephrotic patients, namely, irritability, relative anorexia and lethargy. Euphoria was observed in one patient; marked social withdrawal in another. With the onset of diuresis, rather striking improvement in personality, increased appetite, and prominent brown pigmentation of the periorbital areas—"dark circles"—were noted. Similar changes have been observed with diuresis from any cause. Marked lethargy and irritability during diuresis either accompanied an electrolyte disturbance or occasionally indicated intercurrent infection.

A search for obvious clinical features favoring a diuretic response has been unrewarding. Neither the age at onset nor the duration of disease appear to have exerted any influence upon response. A low salt diet did not favor diuresis (table 2), and low or very low salt diets predisposed patients to relatively serious electrolyte disturbances which may have interfered with diuresis.

Abdominal paracentesis was performed before, during or after ACTH administration in 12 of 38 courses in which diuresis subsequently occurred. This procedure was necessitated by severe, increasing

TABLE 2

RELATION OF Na-CONTENT OF DIET TO ACTH-INDUCED DIURESIS

	Low Salt[1]	Ward Diet[2]
A. All Courses		
Diuresis	20	18
No Diuresis	14	4
B. Excluding Courses of Less than 8 Days' Duration		
Diuresis	19	18
No Diuresis	7	3

[1] Low salt diet includes "salt free" and "low salt" categories (5–30 mEq. Na^+, 0.5–1.0 gm. NaCl/day).
[2] Ward diet is usual hospital diet without added salt (up to 90 mEq. Na^+, 3.0–5.5 gm. NaCl/day).

ascites. Marked ascites is accompanied by anorexia, abdominal discomfort, frequent umbilical herniation, impaired pulmonary expansion predisposing to anoxia and pulmonary infection, and perhaps by decreased renal blood flow and glomerular filtration rates which have been demonstrated to accompany increased abdominal pressure.[11]*

Spontaneous diuresis occasionally has been observed to follow paracentesis, or loss of edema may result from continued drainage from the wound. When paracentesis was performed during treatment, drainage through the wound, which was never sutured, had ceased prior to onset of diuresis. In these patients diuresis began, on the average, on the 9th day of ACTH therapy, as in the 26 courses in which paracentesis was not done. Paracentesis was also performed before, during or immediately after 6 of the 9 courses of ACTH (Group IIA), in which diuresis failed to occur.

A consistent weight gain was regularly observed during ACTH therapy. In the 26 courses followed by diuresis in which the weight changes were not complicated by paracentesis, the average weight increment during therapy was 1.1 kg., a gain of 5% over the average pretherapeutic weight. With diuresis, approximately 25% of pretherapeutic weight (5.6 kg.) was lost. In this group, diuresis usually began during the 9th day of therapy, was maximal 72± hours later (2 days after treatment was stopped) and continued for at least another 5 to 6 days.

* Detailed studies of glomerular filtration rate (GFR) (inulin), and renal plasma flow (RPF) sodium p-aminohippurate (PAH) have been carried out before, during and after abdominal paracentesis in 2 nephrotic children in whom GFR's were 11 and 53 cc./min./sq.m., respectively, and initial intra-abdominal pressures measured 250 and 110 mm. H_2O. Paracentesis resulted in reduction of intra-abdominal pressure to 70 and 100 mm. H_2O, respectively. No striking changes in renal functions were apparent either during or immediately after paracentesis. A very transient (15 min.) increase of GFR (from 50 to 67 cc./min.) occurred in the second patient and was associated with elevation of the filtration fraction (0.20 to 0.24).

2. Duration of Remission: The persistence of clinical remission at the arbitrary time chosen for the analysis of this data (July 1951) is indicated in chart 3. In 3 of 7 patients who developed recurrences (table 3) but received no further ACTH therapy spontaneous diuresis subsequently occurred, usually followed by prompt secondary recurrence of edema. Fleeting episodes of alternating edema and diuresis have been observed rather frequently in the several weeks following ACTH-induced diuresis, if a mild upper respiratory infection occurred. Remissions have lasted for more than 6 mo. in 12

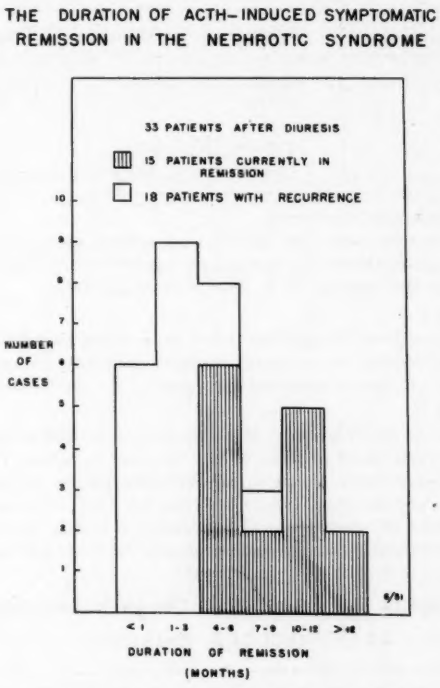

CHART 3. Total area of chart includes 33 patients following diuresis. Open areas indicate recurrences; hatched areas, persistent remissions, Majority of relapses were observed within 4 mo. of diuresis.

TABLE 3

FURTHER RESULTS IN 18 PATIENTS WHO DIURESED AND SUBSEQUENTLY HAD RECURRENCE

No. Patients	Therapy	Response		Clinical Remission†	Dead
		Diuresis	No Diuresis*		
11	ACTH‡	9	1	7§	1
7	None	3	4	1	0

* Continued active disease.

† Clinical remission—asymptomatic, edema-free. Variable proteinuria, blood chemistries.

‡ 1 patient received cortisone, not ACTH, and diuresis resulted.

§ 1 patient has recently had another recurrence.

TABLE 4

URINE VALUES BEFORE AND AFTER ACTH THERAPY

12 Hr. Excretions	Diuresis Group		No Diuresis* Group	
	Average Value		Average Value	
	Before	After	Before	After
RBC (Million)	8.4† (20)	0.6 (12)	13.4 (4)	0.3 18.1 (2)
Total Protein (gm.)	1.2 (26)	0.7‡ (11)	1.90 (4)	1.0 (1)

* Too few data to analyze; cited for interest.

† Two values at both extremes have been omitted from average; these $\times 10^6$ were before: 196, 77; after: 0.4, 0.3. Numbers in parentheses refer to number of patients contributing to average.

‡ Three patients had less than 0.04 gm./12 hr. None were protein-free.

patients to date, and in 6 of these for approximately 1 yr. or more. Urinalysis was normal, without proteinuria, in 4 of these patients. In a group of nephrotic patients of this size spontaneous remissions with disappearance of clinical symptoms and signs of the disease are likely to occur in a certain number each year.

3. Failure of Diuresis: In the 18 instances in which diuresis was not induced, 9 courses (Group IIB) were of less than 7 days' duration. Four of these occurred in patients treated before adequate dosage schedules were devised, while 5 were in patients whose therapy had to be abruptly stopped because of the appearance of some complication. In Group IIA, one patient died on the 10th day of therapy. Ill-defined systematic infections appeared on cessation of therapy in 3 patients, one of whom died 4 days later with bacteremia, peritonitis and pneumonia due to E. coli, resistant to aureomycin.

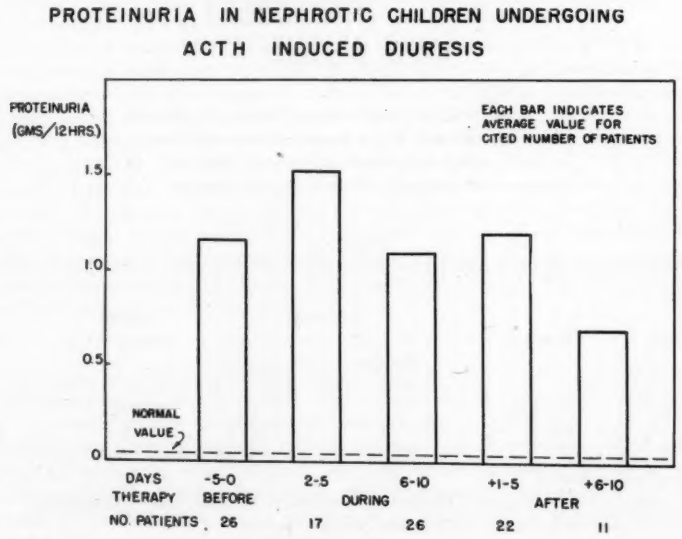

CHART 4

Intercurrent infection frequently causes an exacerbation of the nephrotic syndrome in relatively nonedematous patients, or interferes with or interrupts diuresis in edematous patients. Hypertension and hypotonicity with convulsions in another patient required reparative therapy which may have interfered with diuresis. One patient was nonedematous when treatment was started, gained slightly during therapy, returning to initial weight after treatment was stopped. Diuresis failed to occur in 3 courses without apparent reason.

B. Physiologic Responses

1. Eosinophiles: The average eosinophile count of the 45 nephrotic patients prior to therapy was 413 mm^3, based on 163 observations. With therapy a minimum of 80 to 90% decrease in circulating eosinophiles was observed. In most instances, counts ranged from 0 to 11/mm^3.

TABLE 5

SERUM VALUES BEFORE AND AFTER ACTH THERAPY

Response	Diuresis		No Diuresis*	
Determination	Average Value†		Average Value	
	Before	After	Before	After
NPN mg./100 cc.	37‡ (37)	32 (38)	47 (9)	40 (9)
Serum Protein gm./100 cc.	3.7 (31)	4.4 (27)	4.2 (5)	4.0 (5)
pH	7.32 (35)	7.38 (36)	7.32 (7)	7.35 (7)
[CO_2] mM/l.	22.1 (37)	26.6 (37)	20.8 (9)	23.5 (8)
[Na] mM/l.	139 (35)	143 (35)	136 (6)	136 (9)
[K] mM/l.	4.8 (33)	4.3 (37)	4.8 (6)	4.3 (8)
[Cl] mM/l.	106 (34)	103 (36)	101 (8)	101 (8)
Ca, mg./100 cc.	7.7 (33)	7.6 (34)	6.8 (7)	6.8 (6)
P, mg./100 cc.	5.6 (31)	4.8 (34)	6.1 (6)	5.5 (5)
Cholesterol mg./100 cc.	644 (29)	417 (29)	592 (6)	533 (3)

* Nine courses of longer than 8 days' duration (Group IIA).

† An average value for several observations before therapy and the last value prior to discharge during or after diuresis were used to compute these data. Each patient, therefore, was only counted once in each average. Numbers in parentheses refer to number of patients.

‡ Twenty-two observations over 40 mg./100 cc.

In 6 out of 47 completed courses absolute reduction of eosinophiles to zero did not occur. In these, despite considerable variability, levels below 30/mm³ were observed at some stage of therapy. The average drop in circulating eosinophiles was actually more striking in Groups IIA and IIB in whom diuresis did not occur than it was in Group I in whom it did.

2. Effects on Urine: Slight hematuria was present in most patients of this series (table 4). Two patients with marked hematuria and all other characteristic features of the nephrotic syndrome had excellent responses to ACTH therapy and rather striking reduction of hematuria. Proteinuria was somewhat diminished following diuresis on the average (table 4, chart 4); while in 3 patients it fell to within normal limits (12 to 30 mg./12 hr.). Complete cessation of proteinuria was not observed during therapy, but has been noted after several months in 4 cases with ACTH-induced clinical remissions.

3. Chemical Constituents of the Serum: Average values for various serum components before therapy and 6 to 10 days after its completion are indicated in table 5. Data for the diuresis group (Group I) and for the nondiuresis group (Group II) are included.

(a) Total Serum Protein: In most instances little change in concentration of total serum protein was observed until diuresis was completed. This is consistent with observations of Luetscher et al.[32] With completion of diuresis, an average increase of approximately 0.7 gm./100 cc. was observed within 1 wk.*

TABLE 6

VARIATIONS IN SEVERAL SERUM COMPONENTS WITH THERAPY

Day*	NPN mg./100 cc.		Cholesterol mg./100 cc.		Na mM/l.		K mM/l.	
	Ave.	No. Observations	Ave.	No. Observations	Ave.	No. Observations	Ave.	No. Observations
Group I. Diuresis								
−5–0	36	53	644	29	139	35	4.8	33
0–2	50	14			137	20	5.2	17
3–7	47	39	646†	18	138	55	4.5	50
8–10	36	29	511‡	22	141	38	3.9	31
†0–2	45	12	469§	20	144	16	3.5	17
†3–5	31	19	389**	13	142	21	4.1	24
Group II. No Diuresis								
−5–0	47	10	592	6	136	6	4.8	6
0–2	53	3			135	3	3.7	3
3–7	74	9	675†	5	132	5	5.2	7
8–10	69	4	585‡	2	129	2	5.5	2
†0–2	65	3			141	2	4.8	2
†3–5	50	7			136	4	3.1	3

* Where minus sign indicates pretherapeutic, and plus sign post-therapeutic days; no prefix, during therapy.

† Days 1–5. ‡ Days 6–10. § Days +1–5. ** Days +6–9.

* In nephrotic patients with increased serum lipoproteins, measurements of specific gravity for determining serum proteins are grossly inaccurate. Kjeldahl determinations are satisfactory, although the use of the usual nitrogen conversion factor (6.25) is questionable.[33] Since fractional "salting-out" technics commonly used in clinical laboratories provide markedly erroneous values for serum albumin and globulin, these fractions are not usually determined in this clinic. Immunochemical methods[34] for determining serum albumin will obviate this difficulty. These reveal extremely low values for serum albumin in nephrotic patients.[35]

Plasma volumes (PV), using the dye T-1824 and an acetone extraction technic,[16] were satisfactorily determined in 7 courses immediately before therapy and again after diuresis was completed. An insignificant average increase from 1.17 l./sq. m. to 1.28 l./sq. m. was observed with diuresis. In 2 patients the PV decreased; in one there was no change; in 4 it increased. In these patients an average increase in serum protein concentration from 3.45 to 4.42 gm./100 cc. (+28%) occurred. The increase in total circulating protein, from 40.7 gm./sq. m. to 56.3 gm./sq. m. (+38%), appeared to be more significant than consideration of either plasma volume or serum protein concentration alone might indicate.

(b) Nonprotein Nitrogen (NPN): Azotemia was not a prominent feature of either group

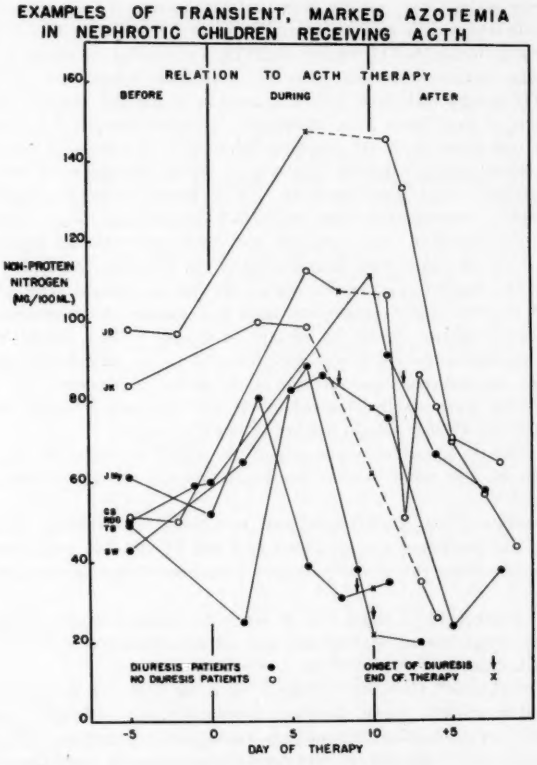

CHART 5

prior to therapy (table 5). During the period of treatment, slight azotemia usually developed with subsequent reduction when ACTH therapy was discontinued. The trend of NPN values during therapy is indicated in table 6. Somewhat more marked azotemia during therapy was noted in Groups IIA and IIB than in Group I. This observation suggests that decreased renal reserve due to greater nephron damage may have been present in these nonresponding groups. In several patients with initially elevated NPN, rather alarming azotemia was observed during therapy, but usually subsided within 2 wk. (chart 5). With severe azotemia, a low protein, high carbohydrate diet was usually substituted for that being consumed. No other treatment was used.

(c) Cholesterol: Serum cholesterol values fell slightly near the end of the period of therapy, and this fall usually continued during the period of diuresis (table 6). In patients of Group II, no definite change in serum cholesterol was apparent; however, there were too few observations for valid interpretation.

(d) Serum Electrolytes: Certain trends in serum electrolyte patterns were observed during therapy. Except for cases in which electrolyte complications developed, the changes were slight, but fairly consistent.

CO_2 and pH: Initial values for serum pH and CO_2-content were slightly reduced in the average nephrotic patient, while normal or slightly elevated average values were observed toward the end of or following therapy. Severe acidosis was noted in 3 patients of Group I on admission. In all, 9 patients in this group who subsequently exhibited a diuresis had pH below 7.25 and 6 had [CO_2] less than 20 mM/l. on admission. Seven patients with coexistent acidosis, azotemia and anemia, a triad which suggests morphologic renal damage and possible poor prognosis,[7] responded favorably to ACTH therapy. Four of the 8 patients of Group IIA also manifested this triad on admission. Patients with severe acidosis were usually given oral supplements of the 3 main cations as $NaHCO_3$, K-acetate, and Ca-lactate in daily amounts of approximately 18 mM, 15 mM and 3 gm., respectively. If alkalosis appeared during ACTH therapy $NaHCO_3$ was omitted, K-acetate was changed to KCl and Ca-lactate was continued. Alkalosis was not uncommon toward the end, and/or following cessation of ACTH therapy. pH above 7.45 was noted in 10 patients, [CO_2] higher than 30 mM/l. in 16, and of these, 5 were above 35.0. Although no definitive symptoms accompanied the marked alkalosis, it was considered clinically important because of distortion of intracellular electrolyte patterns usually accompanying alkalosis and because of the possibility of tetany. In the severe instances, KCl and $CaCl_2$ were given orally for 2 to 3 days in doses of approximately 30mM and 3 gm./24 hr. Neither intravenous therapy nor NH_4Cl administration were required. Hyponatremia was associated with reduction in [CO_2] and pH—i.e., "metabolic" acidosis. Hypokaliemia and hypochloremia were usually associated with increased [CO_2] and pH—i.e., "metabolic" alkalosis.

Sodium: Since the method of measuring serum Na has an intrinsic error of about 2%,[8] it is extremely difficult to assess slight changes associated with therapy. An insignificant average increase in serum Na occurred during therapy in patients of Group I. This change was not necessarily indicative of an impending favorable response. About 25% of patients subsequently undergoing diuresis manifested hyponatremia near the end of the period of therapy (*vide infra*). Maximum increases in serum Na were usually observed in the 48 hr. period following cessation of ACTH treatment, irrespective of whether diuresis had begun or was to occur.

In 8 courses in Group I, sodium values rose to 150 mM/l. or higher. In 4 out of 9 courses of Group IIA, sodium was 140 mM/l. or more shortly after therapy was discontinued; however, diuresis did not occur.

Potassium: A consistent fall, possibly significant, in serum K was observed during ACTH therapy in Group I (table 6). The lowest average values (3.9 and 3.5 mM/l.), were observed in the 48 hr. period after completion of the full 10 day course. No consistent changes in serum K in Group II were noted.

Chloride: The tendency for a slight fall in serum Cl values toward the end of therapy was consistent with the trend toward hypokalemia and alkalosis observed in Group I. No consistent changes in serum Cl of Group II were observed.

Ca and P: Hypocalcemia* (less than 4 mEq./l. or 8 mg./100 cc.) is commonly present in the nephrotic syndrome in children: tetany, however, is extremely rare, although it may be induced by K^+ administration[17, 18] or may occur terminally in association with uremia. The hypocalcemia was usually aggravated by ACTH therapy and was particularly evident in association with hyponatremia. The initial calcium deficit does not result from hypercalcuria and is not readily repaired by oral administration of calcium salts and vitamin D;[10] however, these substances were routinely administered to the nephrotic patients—particularly during periods when additional potassium intake was prescribed.

Abnormalities in serum P are uncommon. The hyperphosphatemia characteristic of advanced renal disease in adults is only rarely observed in the nephrotic patient, even though azotemia and acidosis may be present. No specific changes in serum inorganic P were noted during ACTH therapy.

4. Effect on Discrete Renal Functions: These have been reported in part.[5] Clearance of a constant infusion of inulin was taken as a measure of glomerular filtration (GFR); of PAH at low blood levels as a measure of (RPF) and at high levels, of maximal tubular excretory capacity, (TmPAH).

* The proportion of ionized or "free" Ca in the serum of nephrotic patients is unknown.

Satisfactory determinations are available in 8 patients before and after diuresis. The data are recorded in table 7. In general, ACTH-induced diuresis was characterized by significant improvement in GFR and the filtration fraction. Slight increase of TmPAH and decrease of RPF were noted. These data are consistent with those of other observers.[3] Repeated determinations performed before, during and after ACTH treatment and diuresis in 4 children indicated that an increased GFR might be observed immediately prior to onset of diuresis as noted by Barnett et al.[2] but apparently was not essential to initiate diuresis.[5] Plasma volume determinations using Evans Blue dye, T-1824, indicated that both an increase in GFR and diuresis could occur without measurable change in plasma volume.

TABLE 7

RENAL FUNCTION STUDIES* BEFORE AND AFTER ACTH-INDUCED DIURESIS

	Patient		Date	Mo.' Duration Disease	Wt. (kg.)	Glomerular Filtration Rate	Renal Plasma Flow	Max. Tubular Excretory Capacity	Filtration Fraction	RPF/Tm	GFR/Tm	Volume Distribution (Thiosulfate) L./sq.m.	Plasma Volume L./sq.m.[1]	Serum Protein gm./100 cc.	Total Circulating Protein[2] gm./sq.m.
1	GB	Ia	12/5/49	2.0	17.70	33						8.3	—		
		b	12/27/49	2.8	11.88	78	325	55	0.21	5.9	1.1	3.2	—		
2	RB	Ia	3/9/50	11.0	18.71	19	136	9	0.14	14.5	2.1	6.2	1.30	2.79	36.3
		b	4/3/50	12.0	13.37	51	127	9	0.30	14.5	4.6	3.7	1.48	4.15	61.4
3	SJ	Ia	3/23/50	3.1	23.25	35	296	30	0.12	9.9	1.1	6.0	0.97	3.46	33.6
		b	4/13/50	4.0	21.27	52	264	30	0.20	8.9	1.6	7.4	1.18	4.67	55.1
		IIa	11/27/50	11.1	28.95	27	269	30	0.10	9.0	0.9	11.4	0.87	3.04	26.5
		b	12/18/50	11.9	21.93	38	224	44	0.17	5.1	1.1	6.8	1.26	4.19	52.8
4	JMa	Ia	5/25/50	4.0	23.74	20	240	32	0.08	7.5	0.7	7.2	1.24	3.78	46.9
		b	6/15/50	4.7	15.62	68	279	37	0.24	7.5	1.5	4.4	0.99	4.26	42.2
5	CP	Ia	6/5/50	4.5	10.32	19	85	8	0.23	10.2	2.6	3.5	1.37	4.47	61.2
		b	6/22/50	5.2	8.86	43	215	22	0.21	9.7	1.9	2.4	1.39	4.86	67.6
6	DF	Ia	10/16/50	3.0	20.3	65	295	50	0.22	5.9	1.3	9.2	1.30	3.71	48.2
		b	11/1/50	3.5	14.7	57	170	43	0.35	3.9	1.3	6.6	1.05	4.92	51.6
7	MP	Ia	1/22/51	14.0	24.68	42	271	34	0.16	7.9	1.2	13.3	—		
		b	2/12/51	14.5	17.45	48	201	24	0.24	8.4	2.0	6.0	—		
8	AS	Ia	3/19/51	1.0	25.50	59	345	60	0.17	5.8	1.0		1.11	2.92	32.4
		b	4/5/51	1.5	19.17	80	302	89	0.26	3.4	0.9		1.63	3.90	63.6
Ave:	Before/sq. m.					35.4	242	31.6	0.15	7.7	1.1		1.17	3.45	40.7
	After/sq m.					57.1	234	39.2	0.24	6.0	1.5		1.28	4.42	56.3
	Per Cent Change					+61%			+60%				+9%	+28%	+38%
Normal Values/sq. m.						76±15	364 ±69	42 ±10	0.21 ±0.05	9.0 ±3.5	2.1 ±0.2		1.20	6.0–7.0	72–84

a =before b=after

[1] Plasma volume/sq. m. surface area as determined with modified Evans blue dye dilution technic.

[2] Total circulating protein/sq. m. surface area from $PV_{L/M^2} \times S.P.\ g/L = TCP\ g/M^2$.

* GFR, RPF and TM all per sq m. surface area. Surface area estimated from height and nonedematous weight.

C. Complications of Therapy: The large doses required to produce an effective response may have predisposed patients to complications. Four deaths occurred in association with ACTH therapy. Two resulted from overwhelming infection (E. coli) and 2 were associated with severe hypertension and electrolyte disturbances. Infection, hypertension and severe electrolyte disorders, when present, were considered contraindications to the institution of therapy or indications for its cessation.

1. Infection: Infection was a serious complication in 6 of 56 courses.[20] Excepting the first few courses of ACTH therapy, patients were maintained on antibiotic therapy before and during its administration. If infection was suspected the antibiotic regime was changed—either the dosage increased or a different antibiotic used—and ACTH therapy was stopped. In contrast to classical experience, pneumococcal infections are rare during the nephrotic syndrome in children at the present

time. Infections caused by gram-negative bacilli or Staph. aureus are much more common. This is probably due to alteration of the bacterial flora as a result of the frequent use of antibiotics which are only effective against certain organisms.

In 2 patients, infection occurred toward the end of therapy and did not interfere with subsequent diuresis. Another patient (R. M.) became listless, with fever and marked leucocytosis, after 5 days of ACTH. With more extensive antibiotic therapy and cessation of ACTH therapy, the presumed infection subsided but he did not experience a diuresis. Cellulitis, with marked leucocytosis and negative blood culture, occurred in another patient (J. K.) after 8 days of therapy. The infection responded to intensive antibiotic therapy and cessation of ACTH therapy, but diuresis did not occur. In this instance failure to diurese may have been related to markedly reduced renal function, particularly in view of the fact that a previous 10 day course had also been ineffective. A 4 yr. old girl (C. S.) developed pneumonitis (E. coli and H. influenzae cultured), severe hypertension and hyponatremia during ACTH therapy. Treatment was stopped on 8th day. Convulsions and coma occurred, from which she did not recover. She died 6 wk. later. The 6th patient (K. Z.), a 2½ yr. old girl, developed E. coli peritonitis coincident with completion of a 10 day course of ACTH therapy. There was some question concerning how much aureomycin had actually been consumed in the preceding few days. Despite intensive antibiotic therapy, she died of complications superimposed on peritonitis, 8 days later.

2. Hypertension: This sign is extremely difficult to assess in young children. In most instances, blood pressure was recorded at least twice daily with a cuff covering 2/3 of the upper arm. Pressures more than 20 mm.Hg above an approximate "normal" level for age were considered as beyond the limits of normal deviation. Some slight elevation above this expected standard deviation was frequently encountered. An elevation to 140/100 mm.Hg or higher was considered dangerous and an indication for withholding or stopping ACTH therapy. In 25 of the 45 patients, elevated systolic and diastolic pressures were recorded for at least 3 days before or during therapy. Another 14 had such a rise in systolic pressures alone.

Severe hypertension occurred in 6 patients. Two of these (T. W., a 3 yr., 5 mo. old male, had pressure of 150/110 mm.Hg and C. S., a 4 yr., 7 mo. old female had 204/168 mm.Hg) developed electrolyte complications and convulsions and died, the first within 24 hr., the second after 6 wk. Another patient was given ACTH therapy despite hypertension (12 yr. old female, had pressure of 170/102 mm.Hg), but therapy had to be discontinued on 6th day because of cardiac decompensation and twitching. At this time she had hyponatremia, azotemia and acidosis. Blood pressure rose to 210/120 mm.Hg despite cessation of therapy, and remained elevated. Convulsions occurred 16 days later. These were controlled after several days, left no apparent residua, but she was still edematous at time of discharge.

Another patient (R. M., a 3 yr. old male) whose BP averaged 125/82 mm.Hg before treatment, developed severe hypertension (148/102 mm.Hg) with concomitant infection on 5th day of therapy. ACTH therapy was stopped, and infection and hypertension gradually subsided within the next 2 wk. Diuresis did not occur.

A fifth patient (J. R., 2½ yr. old male) had recorded blood pressures averaging 120/80 mm.Hg before ACTH therapy and rising to 150/105 mm.Hg on 9th day of therapy in association with a poorly defined infection. ACTH therapy was stopped, with prompt fall in BP to 90/60 mm.Hg within 6 days and with satisfactory diuresis.

The sixth patient to acquire severe hypertension (M. deP., 10 yr. old male) had mild hypertension on admission, but on bedrest and veraloid® by mouth, BP gradually fell to 120/80-90 mm.Hg. After 2 to 3 wk., ACTH was administered. Blood pressure rose to 140/110 mm.Hg on 7th day and treatment was stopped on 8th day. Twenty-four hours later it had risen to 162/122 mm.Hg, but gradually fell to 112/88 mm.Hg by completion of diuresis 10 days later. Hypertension has not recurred, despite 3 subsequent courses of cortisone therapy—each followed by diuresis.

3. Severe Electrolyte Disturbance: In 28 of the 56 courses of ACTH therapy, a significant fall in the serum levels of one or more of the electrolytes was observed (chart 6). When reduction of serum levels below 130 mM/l. for Na, 3.0 mM/l. for K, 3.0 mEq./l. for Ca and 90 mM/l. for Cl were observed, undesirable clinical events generally followed.

Sodium: Hyponatremia (serum [Na^+] below 130 mM/l.) occurred as a result of ACTH therapy in 18 of 56 courses. In 10 of these instances diuresis occurred; in 4, hyponatremia was observed in the 24 hr. period immediately preceding the onset of diuresis (chart 7). In 8 patients developing

ELECTROLYTE COMPLICATIONS OF ACTH THERAPY OF NEPHROTIC SYNDROME

PLASMA ELECTROLYTE COMPOSITION

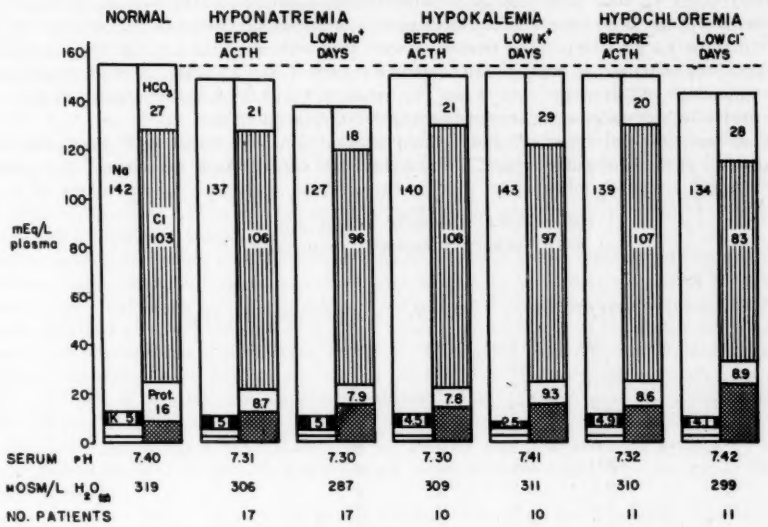

CHART 6

HYPONATREMIA OCCURRING DURING ACTH THERAPY OF THE NEPHROTIC SYNDROME

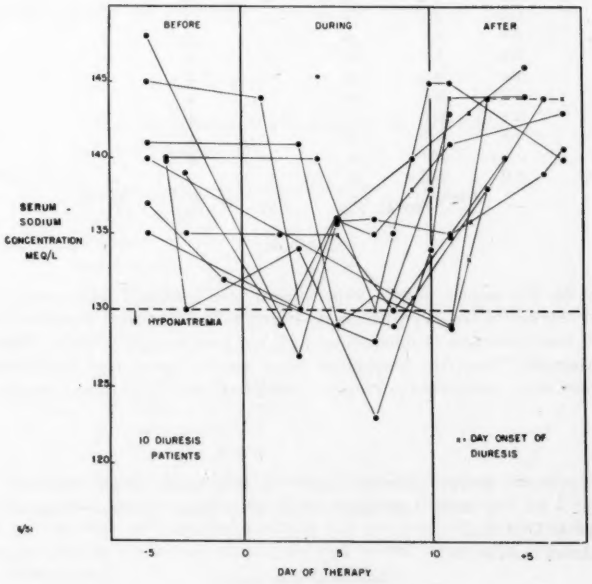

CHART 7

hyponatremia in whom a diuresis did not occur 4 were in Group IIA, 4 in Group IIB. Reduction of serum Na-concentration indicated a reduction in total osmolarity of the extracellular fluid (hypotonicity) (chart 6), since other substances contributing to osmolarity usually were not increased.

Nineteen of the 28 patients who developed electrolyte disturbances were on a salt-free or low salt diet (0.03 to 2.0 gm./day). Nine received a ward diet without added salt. Of 18 patients who developed hyponatremia, 16 were on salt restriction regimes (chart 8). Three of the 4 patients who died following ACTH therapy had serum Na below 125 mM/l. during treatment, in one case associated with hyperkaliemia, in another, associated with hypocalcemia.

When serum Na fell below 125 mM/l. there usually was definite worsening of the clinical state characteristic of the "low salt syndrome,"[21-23] and electrolyte repair therapy was initiated. In 2 patients

LOW SERUM ELECTROLYTE VALUES DURING ACTH THERAPY OF NEPHROTIC SYNDROME

PATIENT	DIET	DIURESIS	LOW Na^+	LOW K^+	LOW Cl^-
J Mc	S F	+	+		
J F	W D	+	+		
P H	S F	+	+		
J R	L S	+	+		
T B	L S	+	+		
S W	L S	+	+		
R M	L S	0	+		
R G[1]	S F	0	+		
R G[2]	S F	0	+		
T W	S F	0	+		
G M	S F	+	+		+
J G	L S	+	+		+
J D	L S	0	+		+
J K	L S	0	+		+
C S	S F	0	+		+
K Z	L S	0	+	+	+
S S	L S	+	+	+	
H S	W D	+		+	+
G R	S F	+		+	+
R D	S F	+		+	+
M P	W D	+		+	+
C H	W D	+		+	
R I	W D	+		+	
S J	L S	+		+	
J My	W D	+		+	
G B	W D	+			—
DIURESIS/TOTAL		18/26	9/17	9/10	7/11

CHART 8

carefully studied by the balance technic, hyponatremia was associated with extracellular dilution plus intracellular transfer of Na only partially equivalent to the calculated depletion of intracellular K. This inferred ionic distortion of intracellular fluid has been thought to be a common feature of the nephrotic syndrome.[24] Since the purpose of repair was to restore total body composition and tonicity of the body water rather than to restore a serum level, both sodium and potassium salts were used.*

* An example of repair therapy, abstracted from a detailed balance study, follows:

J. H., a 2 yr., 4 mo. old male. Cumulative result of 15 days' supplementation of low salt diet with $NaHCO_3$ and $KCOOCH_3$.

1. Supplementation averaged

(Continued next page)

It has been the authors' practice to use the oral route for electrolyte repair, except in the rare emergency situation, since it is usually safe, and although slow (5 to 10 days), quite successful. In most instances, daily administration of sodium (2-3 mM/kg. Na^+) was considered an indication for simultaneous administration of potassium (3-5 mM/kg. K^+) (usually K-acetate) and calcium (usually Ca lactate 2-4 gm./day) salts. With hyperchloremic acidosis, $NaHCO_3$ was used orally in preference to NaCl. This type of repair should not be undertaken unless it is carried out at rates consonant with the relatively slow exchange of base between extracellular fluid and intracellular fluid and within the limits of circulatory adjustments, otherwise pulmonary edema and tetany may occur. With the exception of the patient with hyponatremia and hyperkaliemia who died abruptly on the 10th day of ACTH therapy, the remaining 17 patients achieved normal values for serum Na within 5 to 10 days—often in association with the ACTH-induced diuresis. The apparent ease with which repair may be effected in the nephrotic child contrasts sharply with the difficulties encountered in other hyponatremic states.[26]

When rapidly developing irritability, marked weakness, vague pains, apparent peripheral-vascular collapse, usually without definite electrocardiographic changes, hypotension or tachycardia, were found to be associated with severe serum hypotonicity in the presence of vomiting and/or diarrhea, NaCl was infused slowly as an approximately 0.5 M (3%) solution in accordance with a plan to achieve 50% repair of the extracellular sodium deficit in the 1st 12 hr. KCl or K-acetate were simultaneously infused as an 0.03-0.05 M solution (0.4-0.5%). At that time, if dangerously low values were no longer present and vomiting had ceased, the remainder of the reparative dose was given by mouth within the next 24 to 48 hr.

Potassium: Hypokaliemia ($[K_S^+]$ less than 3.0 mM/l.) was observed in 11 patients, in 10 of whom diuresis occurred. In general, low potassium values were observed toward the end of ACTH therapy (chart 9).

Low values for $[Na_S^+]$ accompanied hypokaliemia in only 2 instances; however, hypochloremia, normal or slightly elevated $[Na_S^+]$ and alkalosis were usually concomitant features (charts 6 and 8). This latter observation is consistent with what Darrow and his associates[27] noted in K-deficient rats. The mechanism may be related to intracellular transfer of available Na^+ in order to replace a deficit of intracellular K. However, balance studies have failed to indicate a significant, continuous loss of K from the body in the nephrotic syndrome.[28–30] A defect in renal regulation of K^+-excretion has been noted in the nephrotic syndrome in children.[31] The resultant severe hypokaliemia occurring during ACTH therapy usually may be readily repaired. An example of such repair is indicated in chart 10.

$Na^+ = 4.6$ mM/kg./day (based on 15 day intake)
$K^+ = 2.5$ mM/kg./day

2. Body weight (Kg.)
   Initial = 12.48
   Final = 14.85
3. Cumulative balance (mM)
   Na = +426
   K (corrected for N) = +337

A large proportion (*ca* 30%) of the retained Na appeared, by calculation, to have entered the intracellular water compartment.

4. Serum (mM/l.)
   Na^+ initial = 114 mM/l.
   Final = 137.5 mM/l.
   K^+ initial = 4.8 mM
   Final = 4.0 mM

It will be noted that the specific purpose of added $NaHCO_3$ and K acetate was repair of striking hypotonicity, not general therapy of the nephrotic syndrome as suggested by Fox and McCune.[23] Although the patient cited above seemed clinically and biochemically improved at the end of this phase of therapy, diuresis did not occur, and he died several weeks later following tetany and a recurrence of hyponatremia.

Chloride: Hypochloremia ($[Cl_a^-]$ less than 90 mM/l.) was observed in 11 patients during therapy (chart 6 and 8). Diuresis occurred despite this event in 7 of these instances. Five of these patients had hypochloremic alkalosis. In the 4 instances in Group II, where diuresis failed to occur, hypochloremia was associated with hyponatremia; however, 4 patients in Group I also had simultaneously low values for both electrolytes preceding diuresis.

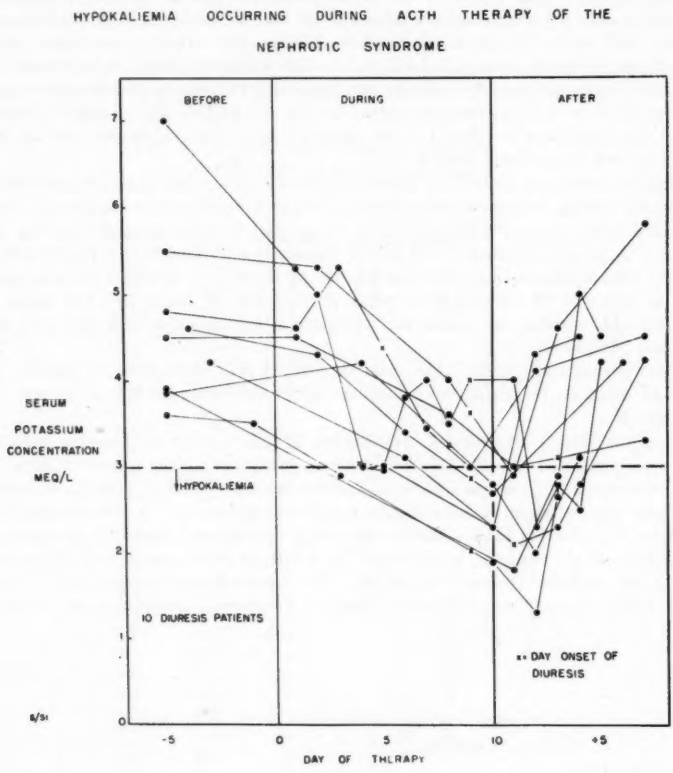

CHART 9

DISCUSSION

Two considerations prompted the trial of adrenocorticotrophic hormone in the nephrotic syndrome. First, the observation that remissions frequently follow acute infections, particularly rubeola,[32, 33] suggested that the response to stress might be the common denominator and might be artificially reproduced by the administration of ACTH. Second, the hypothesis that the basic renal lesion in the disease is an injury caused by the local combination of antigen and antibody in the kidney suggested the trial of an agent known to affect allergic reactions. That ACTH therapy proved to have rather dramatic effects on the disease cannot be taken as proof of either of these ideas, although it is consistent with them.

It is the authors' belief that the increased liberation of adrenal steroids as a result of

ACTH stimulation alters glomerular basement membrane permeability and reaction[34, 35] and leads to improved tubular cell function with secondary renal hemodynamic adjustments. Decreased proteinuria, improved potassium metabolism, and increased excretion of salt and water are associated with the primary changes. In this view, diuresis may be an incidental feature accompanying successful therapeutic response. Accordingly, several patients in the present series were subjected to ACTH therapy although relatively devoid

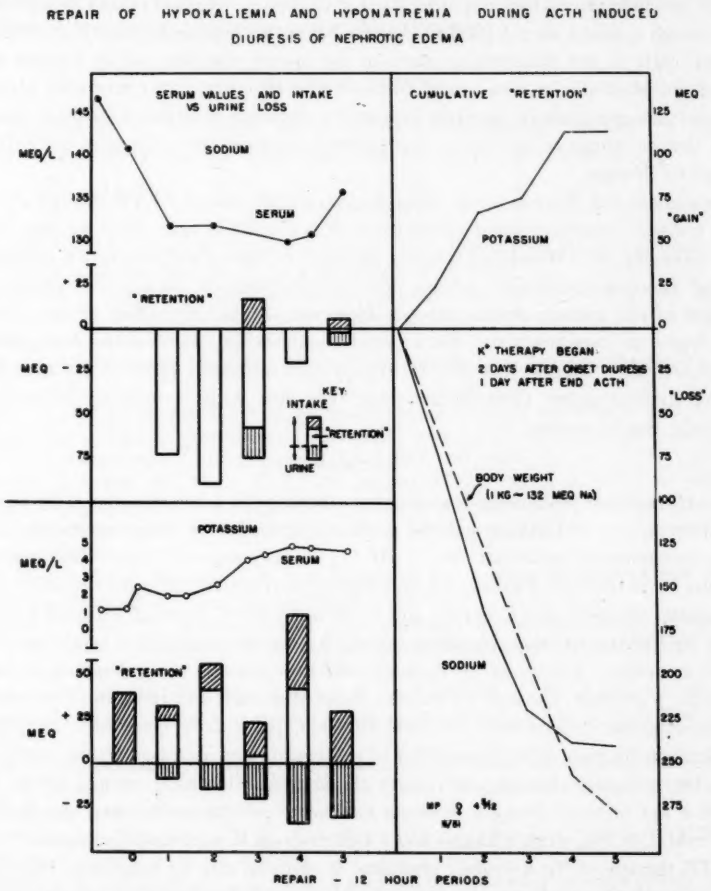

CHART 10. Data from which this chart was constructed were derived from 4½ yr. old girl whose [K_s^+] fell to 1.2 mM/l. on 10th day of ACTH therapy. She presented marked lethargy, weakness, tetany and typical electrocardiographic configuration for hypokaliemia. Hypocalcemia and alkalosis were also present. Repair, favored by diuresis, was effected within 48 hr. by administration of 90 to 110 mM K^+, largely as KCl/24 hr. Both intravenous and oral routes were used. Na^+ intake was limited to 0 to 14 mM/day and 20 to 30 cc. of 10% solution of $CaCl_2$ was given/24 hr.

of edema at the time. The real mechanisms responsible for either diuresis or remission are not yet clear.

It has not been possible to predict which patients will diurese or what factors may favor diuresis. The following appear to favor diuresis: A large dose of ACTH (150 to 200 mg./sq.m./24 hr.) continued for eight or more days; minimal dietary salt restriction (i.e., no added salt); and probably minimal renal parenchymal damage as indicated by reversible renal functional impairment. Although hyponatremia with acidosis and azotemia did not preclude satisfactory response, absence of these particular features seemed to favor it. Although it would seem logical to expect a better therapeutic response if treatment were initiated early in the chronologic course of the disease, the data fail to support such an impression. Markedly impaired renal function may represent either reversible physiologic or irreversible morphologic damage. Persistently impaired function, after many months of active disease, suggests the latter, and patients showing these changes are unlikely to respond to therapy.

It is evident that diuresis is not dependent on withdrawal of ACTH therapy and subsequent transient relative adrenal insufficiency. It is equally obvious from the rate of recurrence following ACTH-induced diuresis, that loss of edema and concurrent improvement in renal function, electrolyte, protein and lipid metabolism, do not necessarily indicate cessation of the primary disease process. However, the fact that these events occur with some degree of consistency and that in several patients the course of the disease has been altered favorably, suggest that ACTH therapy may ultimately prove to be more than an effective diuretic agent. Considerably more time and study is required before such an assessment can be made.

Summary

The clinical and physiologic features characterizing the administration of 56 courses of ACTH therapy to 45 children with the nephrotic syndrome have been reviewed.

The intramuscular administration of ACTH in daily doses of 150 to 200 mg./sq.m./24 hours for at least 8 and usually 10 days resulted in complete diuresis in 38 of 47 (81%) such courses, in 68% of all courses, and in 34 of 45 (75%) patients treated.* Approximately 50% of the patients undergoing diuresis have maintained clinical remissions of three months or longer. Twelve of 16 such patients have been in clinical remission for over 6 months; 6 of these, for over 12 months. Induced diuresis and remission were associated with considerable improvement in renal function, particularly glomerular filtration rate and filtration fraction. Some diminution of proteinuria and increased serum protein levels were observed after diuresis, and serum cholesterol fell toward normal levels. Rather consistent but minimal changes in serum electrolyte patterns were noted. An increase of 2 to 4 mM/l. in Na, slight alkalosis and a fall in serum K were usual responses.

ACTH therapy of the nephrotic syndrome in children may be hazardous. Four patients died as a result of complications associated with therapy. The principal complications were infection, severe hypertension and hypotonicity of the extracellular fluid. Prompt recognition and treatment of these disorders with immediate withdrawal of ACTH therapy required constant vigilance and careful supervision. For this reason, this method of treatment is not considered to be a safe outpatient procedure.

*Similar results have been noted in 29 courses in 26 patients treated, since this report was prepared. In all, of 71 patients treated, 33% have been in remission for approximately 1 yr., and an additional 9% for at least 6 mo., to date.

The mechanisms responsible for diuresis and remission induced by ACTH therapy are not yet clear. Adequate dosage, normal diet without salt restriction but without added or excessive salt, and possibly a limited period of reduced renal function appear to favor diuresis. Neither the age of the patient nor the (chronologic) duration of disease appear to influence the outcome in children.

Although ACTH therapy may not effect a cure, it does appear to alter the course favorably in a relatively significant number of patients treated, and therefore at the present time appears to be the treatment of choice for the active phase of the nephrotic syndrome in children. A preventive or curative agent is still to be found.

Acknowledgment

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References

1. Farnsworth, E. B., Metabolic changes associated with administration of adrenocorticotropin in nephrotic syndrome, Proc. Soc. Exper. Biol. & Med. **74**:60, 1950.
2. Barnett, H. L., and others, Effect of adrenocorticotropic hormone on children with nephrotic syndrome. II. Physiologic observations on discrete kidney functions and plasma volume, J. Clin. Investigation **30**:227, 1951.
3. Riley, C. M., Nephrotic syndrome: Effect of adrenocorticotropic hormone, Pediatrics **7**:457, 1951.
4. Rapoport, M., and others, Effect of adrenocorticotropic hormone on children with nephrotic syndrome. I. Clinical observations in 34 children treated with ACTH and observations on 4 of these children treated with cortisone, J.A.M.A. **147**:1101, 1951.
5. Metcoff, J., Kelsey, W., Rance, C. P., and Janeway, C. A., Effects of ACTH on pathologic physiology and clinical course of nephrotic syndrome in children, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, chap. 1, p. 148.
6. Luetscher, J. A., Jr., Deming, D. B., and Johnson, B. B., Treatment of nephrosis with pituitary adrenocorticotrophin, J. Clin. Investigation **30**:1530, 1951.
7. Metcoff, J., Kelsey, W. M., and Janeway, C. A., Nephrotic syndrome in children: Interpretation of its clinical, biochemical, and renal hemodynamic features as variations of single type of nephron disease, J. Clin. Investigation **30**:471, 1951.
8. Wallace, W. M., Holliday, M., Cushman, M., and Elkinton, J. R., Application of internal standard flame photometer to analysis of biological material, J. Lab. & Clin. Med. **37**:621, 1951.
9. Ham, T. H., Examination of urine sediment by Addis qualitative and semiquantitative methods, in a Syllabus of Laboratory Examinations in Clinical Diagnosis, Cambridge, Mass., Harvard University Press, 1950, p. 276.
10. Peters, J., and Van Slyke, D. D., Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 683.
11. Bradley, S. E., and Bradley, G. P., Effect of increased intra-abdominal pressure on renal function in man, J. Clin. Investigation **26**:1010, 1947.
12. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L., Treatment of nephrosis with concentrated human serum albumin. I. Effects on proteins of body fluids, J. Clin. Investigation **28**:700, 1949.
13. Armstrong, S. H., Jr., Budka, M. J. E., and Morrison, K. C., Preparation and properties of serum and plasma proteins. XI. Quantitative interpretation of electrophoretic schlieren diagrams of normal human plasma proteins, J. Am. Chem. Soc. **69**:416, 1947.
14. Gitlin, D., Davidson, C. S., and Wetterlow, L. H., Quantitative estimation of serum albumin in human body fluids by direct titration with specific horse antiserum, J. Immunol. **63**:415, 1949.

15. Gitlin, D., and Janeway, C. A., Immunochemical study of albumins of serum, urine, ascitic fluid, and edema fluids in nephrotic syndrome, J. Clin. Investigation **31**:223, 1952.
16. Chinard, F. P., and Eder, H. A., Determination of concentration of dye T-1824 in normal and lipemic plasmas, J. Exper. Med. **87**:473, 1948.
17. Engel, F. L., Martin, S. P., and Taylor, H., On relation of potassium to neurological manifestations of hypocalcemic tetany, Bull. Johns Hopkins Hosp. **84**:285, 1949.
18. Metcoff, J., Unpublished observations.
19. Emerson, K., Jr., and Beckman, W. W., Calcium metabolism in nephrosis. I. Description of abnormality in calcium metabolism in children with nephrosis, J. Clin. Investigation **24**:564, 1945.
20. Editorial, ACTH and cortisone in infection, New England J. Med. **245**:75, 1951.
21. Schroeder, H. A., Renal failure associated with low extracellular sodium chloride: Low salt syndrome, J.A.M.A. **141**:117, 1949.
22. Mariott, H. L., Water and Salt Depletion, Publication no. 32, American Lecture Series, Monograph in American Lectures in Physiology, edited by R. F. Pitts, Springfield, Ill., Charles C Thomas, Publisher, 1950.
23. Soloff, L. A., and Zatuchni, J., Syndrome of salt depletion induced by regimen of sodium restriction and sodium diuresis, J.A.M.A. **139**:1136, 1949.
24. Fox, C. L., Jr., and Slobody, L. B., Tissue changes in nephrotic syndrome: Demonstration of potassium depletion, PEDIATRICS **7**:186, 1951.
25. Fox, C. L. Jr., and McCune, D. J., Electrolyte changes in nephrosis: Occurrence of diuresis following administration of sodium and potassium salts, Am. J. M. Sc. **216**:1, 1948.
26. Waterhouse, C., Kentmann, E., and Fenninger, L. D., Studies on mechanism of edema formation in patients with low serum electrolytes, J. Clin. Investigation **30**:681, 1951.
27. Darrow, C. D., Schwartz, R., Iannucci, J. F., and Coville, F., Relation of serum bicarbonate concentration to muscle composition, J. Clin. Investigation **27**:198, 1948.
28. Loeb, R. F., and others, On mechanism of nephrotic edema, J. Clin. Investigation **11**:621, 1932.
29. Hoffman, W. S., and Post, W. E., Influence of mineral metabolism upon nephrotic edema, J. Clin. Investigation **12**:613, 1933.
30. Metcoff, J., and others, Unpublished observations.
31. Metcoff, J., Rance, C. P., and Nakasone, N., Observations on renal mechanisms for sodium and potassium excretion in ACTH-induced diuresis of nephrotic edema, J. Clin. Investigation **30**:661, 1951.
32. Blumberg, R. W., and Cassady, H. A., Effect of measles on nephrotic syndrome, Am. J. Dis. Child. **73**:151, 1947.
33. Janeway, C. A., and others, Diuresis in children with nephrosis: Comparison of response to injection of normal human serum albumin and to infections, particularly measles, Tr. A. Am. Physicians **61**:108, 1948.
34. Ehrich, W., and Forman, C., Personal communication to the authors.
35. Lauson, H. D., and others, Effect of ACTH on glomerular permeability to albumin in children with nephrotic syndrome, Am. J. Dis. Child., to be published.

SPANISH ABSTRACT

Terapéutica con la Hormona Adrenocorticotrófica (ACTH) del Síndrome Nefrótico en Niños

La experiencia obtenida de la prescripción de 56 series terapéuticas con A.C.T.H., en 45 niños con síndrome nefrótico les permite asegurar a los autores del artículo, que esta terpéutica, aunque no es curativa, actualmente es el tratamiento de elección de la fase activa de la enfermedad.

Los pacientes seleccionados para el estudio terapéutico tenían las manifestaciones clásicas del síndrome nefrótico: edema masivo de principio insidioso asociado con oliguria, proteinuria acentuada, hipoproteinemia, hiperlipemia y en algunos casos hipertensión arterial transitoria. Teniendo en consideración que existen pruebas sugestivas que el síndrome nefrótico es una forma de nefritis y que la diferenciación clínica de "nefrosis verdadera" es arbitraria y probablemente no válida, se incluyeron algunos casos que ocasionalmente presentaron azotemia, hematuria y reducción moderada

de la función renal. Como contraindicaciones terapéuticas se consideró la existencia de hipertensión arterial, infección reciente, desviaciones marcadas de los electrolitos del suero y uremia. El promedio de duración del padecimiento antes de iniciar la terapéutica fué de 5 meses variando de 2 semanas hasta 51 meses. El promedio de edad fué de 3-7/12 años, oscilando entre 1 9/12 y 11 9/12 años. Los cuidados generales fueron reposo en cama, presiones arteriales cuando menos 2 veces al día, peso diario en ayunas y sin ropa, ingestión aproximada de 400 c.c. por metro cuadrado y por 24 horas más el volumen de agua correspondiente al de la orina de 24 horas y vigilancia cuidadosa de signos de infección particularmente de la piel y de las vías respiratorias superiores. La dieta prescrita varió de dieta sin sal a dieta normal sin adición de sal extra, la cual a menudo no fué consumida por completo. Se administró generalmente aureomicina durante todo el período de hospitalización (21 a 28 días) a dosis de 30 a 50 mlgs/Kg/24 horas u otro antibiótico indicado en cantidades similares. La administración de A.C.T.H. se hizo por vía intramuscular a la dosis de 150-200 mlgs. por metro cuadrado de superficie corporal y por 24 horas repartida en candidades iguales e inyectadas intramuscularmente cada 6 horas, durante un periódo de 10 días siempre que fué posible. El cálculo de la superficie corporal se hizo según la fórmula de Dubois, tomando el peso que se supuso tendría el enfermo sin edema, basado en la estimación hecha por los padres o en el peso correspondiente a su estatura obtenida de una gráfica standard en porcentiles.

La respuesta clínica al tratamiento fué la siguiente: se obtuvo diuresis con desaparación completa del edema en 38 ó sea el 68% de un total de 56 tratamientos, pero si se tabulan solo las diuresis completas en los tratamientos de 8 ó más días de duración, que fueron 47, la cifra es de 81% y en lo que respecta a enfermos, 34 de 45 ó sea el 75% respondieron con diuresis completa. En una serie adicional de 29 tratamientos de 10 días dados a 26 enfermos, que trataron los autores desde que su artículo se preparó para publicarse, se indujo diuresis con el 85% de los tratamientos y en el 81% de los enfermos. La diuresis generalmente se inició entre el 8 y 12° días de terapéutica y el edema desapareció totalmente a los 7 días de iniciada la diuresis.

Los cambios de personalidad y de conducta durante el tratamiento fueron en general los mismos que acompañan al aumento del edema del niño nefrótico: irritabilidad, anorexia y letargia. Un enfermo presentó euforia, otro aislamiento social marcado. Al iniciarse la diuresis la personalidad mejoró, aumentó el apetito, y aparecieron "ojeras" bastante notables. Estos cambios han sido observados en las diuresis de cualquier otra causa.

Cuando hubo letargia e irritabilidad acentuadas generalmente existía un trastorno electrolítico u ocasionalmente una infección intercurrente. No hubo influencia favorable de la edad, duración de la enfermedad y la respuesta obtenida. Las dietas pobres o muy pobres en sal predispusieron a los enfermos a serios trastornos electrolíticos que pudieron interferir con la diuresis. En algunas casos hubo que hacer paracentesis abdominal antes, durante, o después de la serie de A.C.T.H. debido a la anorexia, molestia abdominal, hernia umbilical, y la imposibilidad de expansión pulmonar predisponiendo los enfermos a la anoxia y a la infección pulmonar pero no favoreció la inducción de la diuresis. Los pacientes ganaron peso consistentemente durante los tratamientos.

El 50% de los enfermos que hicieron diuresis se mantuvieron en remisión clínica por 3 meses o más, en 12 de 16 casos duró más de 6 meses, y 6 de estos por más de un año. Añadiendo a estos datos los obtenidos hasta el momento en que se escribió este informe, de 71 enfermos tratados en total, 33% han estado en remisión por 1 año aproximadamente y 9% más cuando menos por 6 meses.

La cuenta promedio de eosinófilos sanguíneos fué de 413 por mm^3 en 163 observaciones y se obtuvo un descenso de 80-90% con la terapéutica, oscilando generalmente entre 0 a 11 por mm^3. La caída de eosinófilos fué en realidad más marcada en el grupo en el que no hubo diuresis.

La diuresis y remisión se asoció con una mejoría considerable de la función renal, particularmente de la filtración glomerular y de la fracción de filtración; cierta disminución de la proteinuria y aumento de las proteínas del suero se apreciaron después de la diuresis y el colesterol del suero descendió a niveles normales.

Se apreciaron cambios mínimos pero con cierta persistencia en los patrones electrolíticos, siendo la respuesta usual un aumento del sodio, ligera alcalosis y caída del K del suero sanguíneo.

La terapia con A.C.T.H. en niños con síndrome nefrótico puede ser peligrosa. Cuatro enfermos murieron de complicaciones terapéuticas. Estas fueron principalmente: infecciones, hipertensión arterial e hipotonicidad del líquido extracelular. La infección fué seria en 6 de las series terapéuticas. Si el enfermo ya estaba con antibióticos se aumentaba la dosis o se cambiaba y se suspendía el A.C.T.H. Los gérmenes más comunmente responsables fueron bacilos gram negativos o el estafilococo

dorado, contrariamente al clásico neumococo de antaño, resultado del uso frecuente de antibióticos que solo son efectivos contra ciertas bacterias. Se presentó hipertensión severa en 6 enfermos. Una elevación de más de 20 mm. de mercurio arriba de la cifra normal para la edad del niño se consideró como anormal y fué frecuente encontrar cifras algo más altas. Cuando subían a 140/100 ó más se consideró que eran peligrosas y se suspendía el A.C.T.H. temporal o definitivamente.

En el 50% de los tratamientos se apreció caída significante de los niveles séricos de uno o más de los electrolitos. La reducción del Na indicó una disminución en la osmolaridad total del líquido extracelular (hipotonicidad) pues generalmente las otras substancias que contribuyen a mantenerla no estaban aumentadas. Cuando la reducción de los niveles séricos del Na, K y Cl fué por abajo de 130, 3 y 90 milimolas por litro respectivamente y el Ca de menos de 3 miliequivalentes, generalmente se observaron manifestaciones clínicas indeseables. Cuando el Na descendía abajo de 125 milimolas por litro generalmente se agravaba el cuadro clínico del "síndrome de carencia de sal" y se iniciaba terapéutica con administración de electrolitos, en la mayor parte de los casos, Na y K simultáneamente. Cuando se presentaban rápidamente síntomas de irritabilidad, debilidad marcada, dolores vagos, aparente colapso vascular periférico, usualmente sin cambios electrocardiográficos definitivos, hipotensión o taquicardia, asociados con hipotonicidad severa del suero, en presencia de vómitos o diarrea o ambas se administraba lentamente por vía venosa solución de NaCl con 0.5 Molas, (3%) hasta restituir en las primeras 12 horas un 50% del déficit extracelular de Na.

Simultáneamente se pasaba una solución de KCl o acetato de potasio con 0.03-0.05 Molas (0.4-0.5%) Si en este término las cifras de electrolitos séricos mejoraban y ya no existían vómitos, el resto de la dosis de reparación se daba por la boca durante las siguientes 24 ó 48 horas.

El mecanismo de la diuresis y remisión inducida por el A.C.T.H., no es aún claro. Los autores opinan que el aumento en la liberación de esteroides suprarrenales como resultado de la estimulación del A.C.T.H. altera la permeabilidad y reacción de la membrana basal del glomérulo renal determinando la mejoría de la función de las células de los túbulos y secundariamente la adaptación renal hemodinámica. La disminución de la proteinuria, la mejoría en el metabolismo del K y el aumento de excreción de sal y agua estan asociados con los cambios primarios, siendo la diuresis un fenómeno incidental que acompaña a la respuesta terapéutica efectiva.

Los factores que parecen favorecer la diuresis son la dosificación adecuada del A.C.T.H., la dieta normal sin restricción o adición de sal y, posiblemente, que el periódo de reducción de la functional renal sea limitado.

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MOBILITY OF THE UPPER CERVICAL SPINE IN HEALTH AND DISEASE

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THIS report demonstrates the way in which an unusual roentgenogram led to a diagnosis incompatible with the clinical facts. Further investigation proved this roentgenographic finding to be a normal variant.

Four children were observed with typical clinical findings of forward subluxation of the upper cervical vertebrae on clinical examination. This diagnosis was confirmed by roentgenographic examination of the cervical spine. The clinical status of each patient improved under therapy, but the roentgen changes failed to show comparable improvement or, at times after initial realignment of the vertebrae, showed reversion to the pretreatment positions without the reappearance of clinical symptoms. It was felt, therefore, that these children had either suffered irreversible damage to the ligamentous structures of the cervical spine permitting subluxation or, more probably, demonstrated a pathologic condition superimposed upon a normal roentgenographic variant of the cervical spine.

The four cases present a distinct clinical syndrome: forward angulation of the upper cervical region with an inability to extend the neck to the neutral position, following minor or unknown trauma experienced during an upper respiratory infection. On physical examination a posterior lump was evident high in the cervical region which was painful on pressure. Roentgenograms demonstrated a forward displacement of C_2 on C_3 when the neck was flexed, together with a loss of the normal lordotic cervical curvature. Symptomatic response to treatment was almost immediate, but the roentgenographic displacement persisted. The four cases are presented below.

CASE REPORTS

Case 1: J. A., a 6 yr. old white male, was first seen with complaint of a "stiff neck," at which time a posterior prominence high in the cervical region was noted. Six days prior to admission he had a mild upper respiratory infection characterized by coryza, cough and a slight fever. On awakening following day he complained of a stiff neck. He had suffered no known trauma. Local applications of heat and gentle massage were given and "stiffness" seemed to disappear. The day prior to admission, he suffered an exacerbation of upper respiratory infection and cervical rigidity reappeared.

Physical examination showed an acutely ill, uncomfortable boy who sat erect with head held forward in mid-line; there was a posterior prominence high in cervical region which was painful to pressure. He was able to flex his neck, but could not extend it even to the neutral position. Lateral rotation to R and L was limited to 30°. Pharynx was slightly injected. Remainder of physical examination was normal.

Beta str. hemolyticus was predominant organism on nasopharyngeal culture.

Roentgenograms of cervical spine demonstrated reversal of normal cervical lordosis with forward displacement of C_2 on C_3, which was accentuated in films taken with neck held in acute flexion.

Patient was placed flat in bed and a head halter with 1.3 kg. traction was applied. Antibiotics

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were given to control the respiratory infection. At end of 2 wk., anatomic restoration of cervical spine had been achieved, as judged by roentgenographic evaluation, through maintenance of hyperextension of neck in a plaster collar. A Minerva plaster jacket was worn for 3 wk. and was then replaced with a Schantz collar, which was worn for an additional 3 wk. He was then symptom-free and RG showed less displacement of C_2 on C_3, especially when neck was flexed.

Case 2: G. P., a 3½ yr. old white male, was admitted to hospital with chief complaint of "stiff neck." Roentgenogram of cervical spine made 2 yr. previously because of head trauma demonstrated no abnormalities.

One week prior to admission he became ill with an upper respiratory infection. Symptomatic

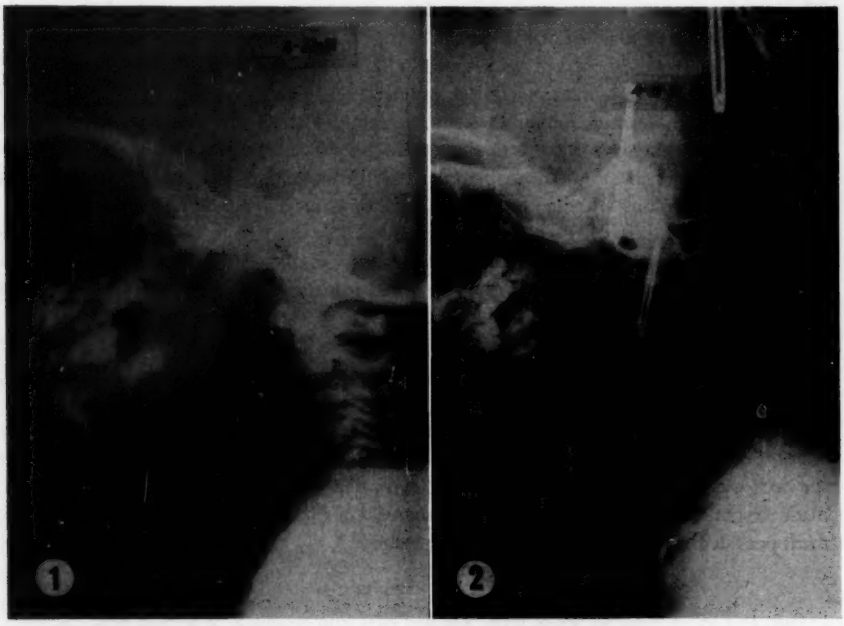


FIG. 1. Case 2 at time of admission. Note forward displacement of C_2 and C_3 and absence of lordosis. RG made with head in position of greatest extension attainable.

FIG. 2. Case 2 after 5 days of head-halter traction. Patient was asymptomatic. Absence of lordosis is still evident but forward displacement of C_2 on C_3 is not as great.

therapy afforded some relief until 2 days prior to admission. He then suffered an exacerbation of symptoms with the onset of fever (38.8°C.). Physical examination showed pharyngitis. Administration of aureomycin resulted in slight improvement in respiratory infection, but next day he awoke complaining of stiff neck. Cervical adenitis had developed and a painful posterior prominence high in cervical region appeared.

Roentgenogram of cervical spine showed loss of normal lordosis and forward displacement of C_2 on C_3 (Fig. 1). This was especially evident in films taken with head held in acute flexion.

Treatment similar to previous case was carried out for 7 days (Fig. 2); the pain subsided. Position of maximal comfort was maintained by means of a Schantz collar (Fig. 3), which caused an unexpected difficulty. He became dependent on collar and, during the next 3 mo., asked frequently that collar be applied "because I feel tired." Weaning him from collar was a problem but was eventually complete. During course of recovery, posterior cervical prominence disappeared (Fig. 4). Roentgenogram, however, showed a persistent significant forward displacment of C_2 on C_3, (Fig. 5).

Case 3: K. H., a 4 yr. old white female, was admitted to the hospital with chief complaint of

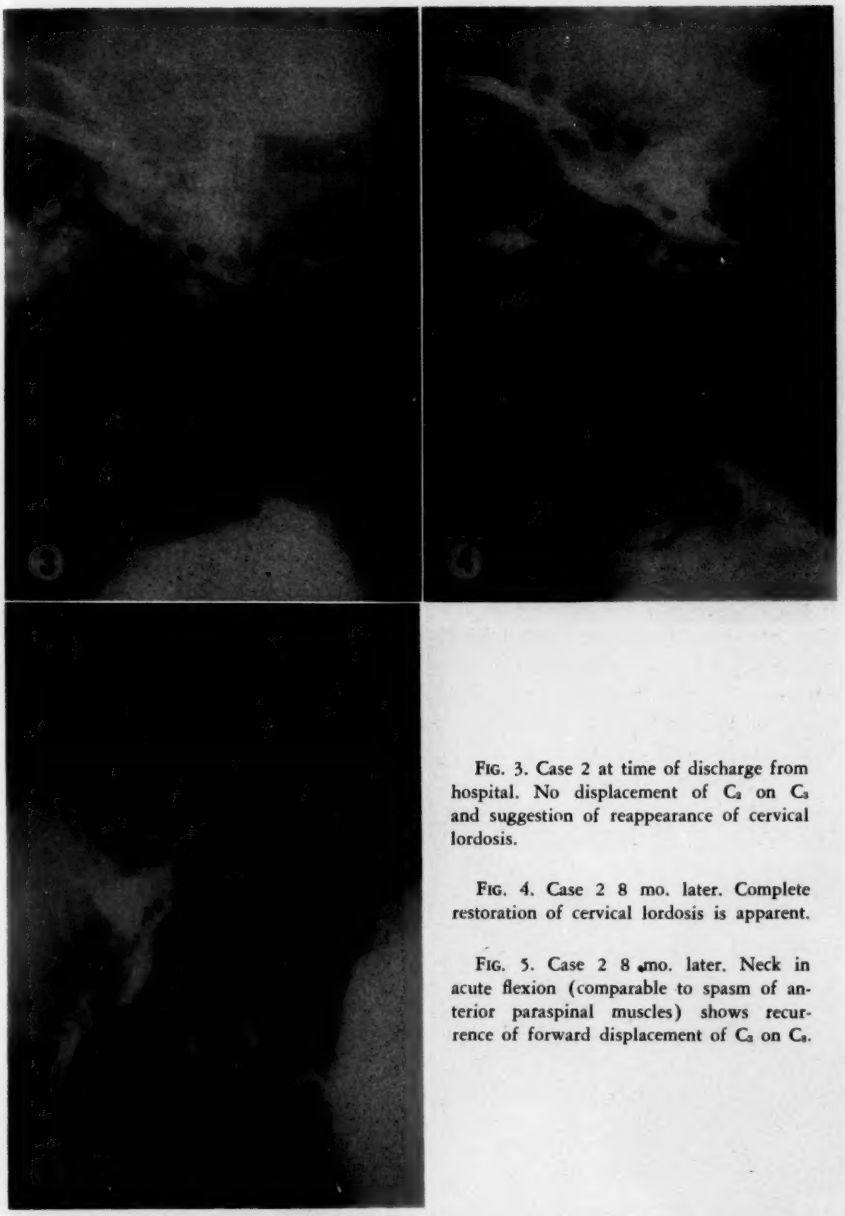


FIG. 3. Case 2 at time of discharge from hospital. No displacement of C_2 on C_3 and suggestion of reappearance of cervical lordosis.

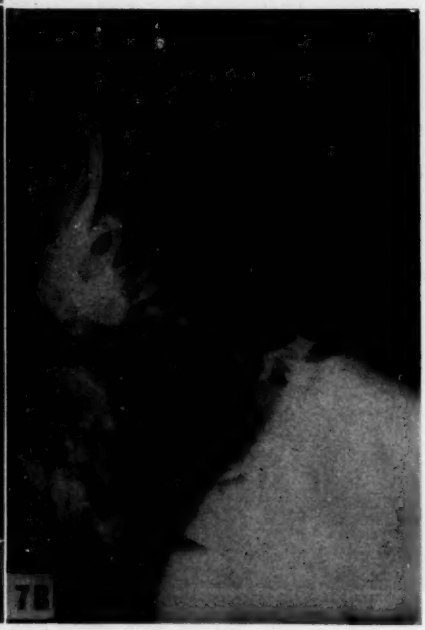
FIG. 4. Case 2 8 mo. later. Complete restoration of cervical lordosis is apparent.

FIG. 5. Case 2 8 mo. later. Neck in acute flexion (comparable to spasm of anterior paraspinal muscles) shows recurrence of forward displacement of C_2 on C_3.

stiff neck of 2 days' duration. Eight months prior to present illness she had suffered a "cold in the neck" which made it difficult to move head. Details of this illness were lacking, but massage and heat to cervical paraspinal muscles seemed to afford symptomatic relief. She remained well until 36 hr. prior to admission when first symptoms of an upper respiratory infection were noted. She was

FIG. 6. RG of cervical spine of normal 4 yr. old girl. Bodies of C_3-C_7 are outlined and from these line is projected through articular facets demonstrating "angle of articulation."

FIG. 7A and B. Cervical spine of normal 4 yr. old boy with neck held in neutral position (A) and in acute flexion (B) where forward displacement of C_2 on C_3 is apparent.



awakened out of a sound sleep by pain in cervical region which was aggravated by attempts to extend neck even to neutral position. A posterior prominence high in cervical region was noted.

Physical examination revealed a slight pharyngeal injection. Head was held forward at a 45°

angle. Flexion of neck was accomplished without difficulty, but extension of neck even to neutral position was limited by pain and muscle spasm. She could rotate chin to 35° on both sides.

Roentgenographic examination demonstrated forward displacement of C_2 on C_3, which was increased in films taken with neck held in flexion. Normal cervical lordosis was absent.

Based on the experience gained from the previous cases, she was placed in a head halter with 3 lb. traction for 7 days, which afforded symptomatic relief within 24 hr. A Schantz collar was applied and maintained for 3 wk. Since then she has been asymptomatic, but RG still show a forward displacement of C_2 on C_3 with normal curvature. Serial RG were almost identical with course shown in figures 1 to 5.

Case 4: R. E., a 4.yr. old white male, was admitted to hospital with a stiff neck of 2 wk.' duration. Three weeks prior to admission, he had had tonsillitis. Two weeks prior to admission, neck was stiff. He held head forward and could not extend it even to neutral position.

Physical examination at time of admission showed same clinical picture already described. Head was held forward at 45°, and a definite prominence was noted high in cervical region posteriorly. Prominence was painful to pressure. Neck could be flexed completely, but it could not be extended even to neutral position. Rotation of head could be accomplished in flexed position with limitation to 30° in both directions.

Roentgenograms of cervical spine showed forward displacement of C_2 on C_3 and a loss of normal cervical lordosis.

Treatment consisted of head halter with 3 lb. traction. This case was unusual in that 17 days were required for symptomatic relief, perhaps because of long duration of condition prior to medical attention. A Schantz collar was applied for 6 wk. Again, symptomatic and clinical restoration to normal was attained; but forward displacement of C_2 on C_3 persisted, especially in those films taken with neck held in flexion. This displacement was as great as that observed at the height of the "disease."

Discussion

There are numerous reports in the literature on the subluxation of C_1 on C_2 (atlanto-axial subluxation) occurring in children during the course of an upper respiratory infection. Yet subluxations of the more caudal cervical vertebrae are rarely mentioned. Pancoast, Pendergrass and Schaeffer[1] mention the occurrence of cervical subluxations in the region of C_2 on C_3 and illustrate the condition with a roentgenogram which portrays an anterior displacement comparable to the cases reported herein. Perhaps the pathogenesis of all cervical subluxations is the same, the site being selected by unknown factors.

The cervical vertebrae compose the most mobile portion of the entire spinal column and are subject to many stresses and strains. Under certain conditions muscular stress may result in subluxation or even fractures. Sullivan[2] has reviewed the atlanto-axial subluxation syndrome, and superficially the present authors' cases seemed to resemble his description. But the findings on roentgenographic examination of the present cases are interpreted as demonstrating normal atlanto-axial relationship.

In the atlanto-axial subluxation syndrome, it is assumed that an inflammatory process of the upper respiratory tract produced relaxation of the transverse ligament of the axis and the articular capsules of the atlanto-axial facet joints. Presumably, spasm of the cervical paraspinal musculature resulting from the pain of the inflammatory process then pulls the atlas forward on the axis to produce the subluxation. The horizontal placement of the facet joints between C_1 and C_2 (Fig. 6) makes this spasm-induced subluxation possible.

There is considerable analogy between this syndrome and the cases observed. A history of a respiratory infection of significant degree can be elicited in each case and the muscle spasm can be clearly demonstrated. Spasm of the cervical paraspinal muscle group results in the disappearance of the normal cervical lordosis and an inability to extend

the neck. The prominence of the spinous process of C_2 is clinical evidence that the structural changes wrought by the muscle spasm are most manifest in the region of C_2 and C_3.

The predilection for forward displacement of C_2 on C_3 is logical. The fulcrum of cervical mobility is at this point. Anatomic investigation demonstrated that the articular facets of C_2 and C_3 lie in a relatively horizontal plane (allowing forward displacement), similar to those between C_1 and C_2 (Fig. 6). All the more caudal cervical facets are more vertically placed, so that forward displacement of these vertebrae must presume some violent trauma or an extreme degree of laxity of the ligamentous structures, which are not presumed to occur under the clinical conditions described.

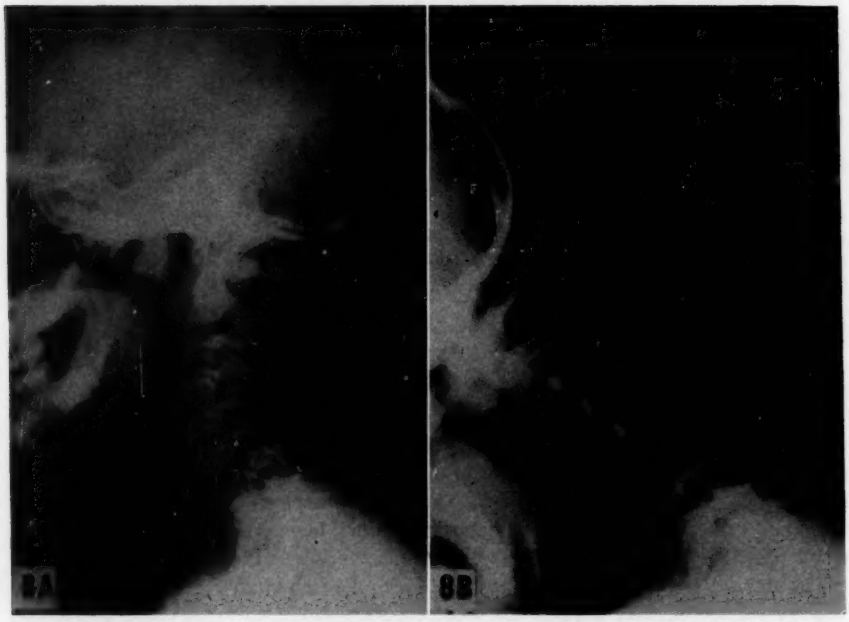


FIG. 8A and B. Cervical spine of normal 6 yr. old boy with neck held in neutral position (A) and in acute flexion (B) where forward displacement of C_2 on C_3 is apparent.

The persistence of the forward displacement of C_2 on C_3 was initially viewed with alarm but was eventually interpreted as a normal variant, since all other manifestations of difficulty had disappeared and the patients were clinically well. Hence, a survey of the cervical spine and its degree of mobility was conducted on children of all ages with no complaints or with a variety of illnesses not related to cervical areas. Roentgenograms were made in all cases with the neck acutely flexed, in the neutral position, and in hyperextension. The subjects varied in age from 10 mo. to 13 yr.

Hadley[3] has demonstrated in adults that, in lateral roentgenographic views of the cervical spine held in mild flexion, some "step-off" (forward displacement) exists between each vertebral body and the subjacent ones. This has been shown by the use of roentgenographic cinematography. Bailey[4] has stated that infants and children show the

same normal finding when the neck is held in flexion, especially at the level of the second and third cervical vertebrae.

The authors examined many "normal" children, and the results are in accord with these reports. The mobility of the cervical spine is greatest between C_2 and C_3 (Fig. 7 and 8). In some cases this forward displacement was as great or greater than in the four cases reported. In general, the longer the neck and the younger the individual, the greater is this degree of mobility of C_2 on C_3. Adult standards of response are attained by 8 years of age in most individuals studied.

It is important to remember that in the initial roentgenogram in the four reported cases only lateral views of the cervical spine in mild flexion could be obtained due to the clinical condition of the patient. Forward displacement of C_2 on C_3 is to be expected in this position, but in these cases it was probably accentuated by spasm of the anterior paraspinal muscles. This spasm was initiated by the existing upper respiratory infection. These findings were initially interpreted, by analogy to the atlanto-axial syndrome, as representing a true subluxation. However, on recovery of these four patients and in normal children of less than 8 years of age, it was in the lateral views made with the neck held in flexion that the subluxation was evident.

This disorder* falls into the category of illnesses in which the use of the laboratory is of value mainly in ruling out other conditions; for example, fractures.

Summary

Four cases of cervical "subluxation" have been presented due to muscle spasm in the cervical region, which occurred during an upper respiratory infection. This syndrome differs from the atlanto-axial subluxation.

Roentgenograms in the diagnosis of this condition may lead to erroneous diagnosis and treatment.

The normal anatomic and functional ranges of the cervical spine were studied and are discussed. The degree of mobility of the cervical spine is greater than previously assumed.

Acknowledgment

The authors wish to thank Dr. Alphonsus L. Grohowski and Dr. E. Forrest Merrill of the Department of Radiology of the Rochester General Hospital for their invaluable aid in interpreting the many roentgenograms.

References

1. Pancoast, H. K., Pendergrass, E. P., and Schaeffer, J. P., Head and Neck in Roentgen Diagnosis, Springfield Ill., Charles C Thomas, Publisher, 1942.
2. Sullivan, A. W., Subluxation of atlanto-axial joint: Sequel to inflammatory processes of neck, J. Pediat. **35**:451, 1949.
3. Hadley, L. E., Roentgenographic studies of cervical spine, Am. J. Roentgenology **53**:173, 1944.
4. Bailey, D. K., Normal cervical spine in infants and children, to be published.

* One of the authors (E.H.T.) has observed the clinical syndrome on occasions other than the 4 cases reported here. One of these is of interest in that cervical rigidity preceded the onset of the upper respiratory infection by 24 hr.

SPANISH ABSTRACT

La Mobilidad de C_2 y C_3 en Condiciones de Salud y de Enfermedad

Los autores reportan cuatro casos de subluxación anterior de las vértebras cervicales superiores cuyos datos eran típicos al examen clínico. El diagnóstico se confirmó por el examen radiológico de la columna cervical. Los casos presentaron un síndrome clínico definido: angulación hacia adelante de la parte superior de la región cervical con imposibilidad de extender el cuello a la posición neutral, después de un traumatismo menor o desconocido realizado durante una infección respiratoria superior. A la exploración física se encontró una saliente posterior en la parte alta de la región cervical que era dolorosa a la presión. Las radiografías mostraron desplazamiento anterior de C_2 sobre C_3 cuando el cuello estaba flexionado, con pérdida de la lordosis cervical normal. El tratamiento sintomático mejoró a los enfermos pero las radiografías no demostraron paralelamente mejoría alguna o bien, después de que las vertebras se alineaban normalmente, volvían a presentar el desplazamiento pero sin la reaparición de los síntomas clínicos.

Por consiguiente se pensó que estos niños habían sufrido una lesión irreversible de las estructuras ligamentosas de la espina cervical que permitía su subluxación o lo que era mas probable, había coexistencia de un proceso patológico sobreañadido a una variación normal de la columna cervical demostrable radiológicamente.

De acuerdo con esta sospecha los autores hicieron un estudiò del grado de movilidad de la columna cervical en niños de meses hasta trece años tomando radiografías en flexión aguda, posición neutra e hiperextensión encontrando el sitio de máxima movilidad entre la C_2 y C_3 y en algunos casos este desplazamiento anterior era tan marcado o aun más que el encontrado en los cuatro enfermos citados. En general, entre mas alto es el cuello y mas joven el niño el grado de movilidad entre C_2 y C_3 es mayor, alcanzándose la movilidad promedio del adulto cuando el niño llega a la edad de 8 años.

La similaridad del cuadro de los enfermos con el síndrome de la subluxación axoatlantoidea es considerable; en ambos existe historia de infección respiratoria de cierta importancia y el espasmo de la musculatura paraespinal cervical, del cual resulta la desaparición de la lordosis normal y la imposibilidad de extender el cuello. Pero la diferencia fundamental estriba en que en los 4 casos reportados el axis y el atlas conservaba sus relaciones anatómicas normales.

Los autores concluyen que es por consiguiente muy importante reconocer el síndrome que presentaron sus enfermos para evitar una terapéutica perjudicial para el enfermo así como establecer el diagnóstico diferencial con la subluxación axoatlantoidea.

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PSYCHIATRIC ASPECTS OF CHANGES IN INFANT AND CHILD CARE

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DURING the last 2 or 3 decades child care has concerned itself with the question of how to raise children who would be emotionally secure and well-adjusted as well as physically healthy. A flood of advice has been directed toward parents as to the "best" psychologic methods of handling children.

I wish to draw attention to the problems involved in deliberately changing child-rearing customs, particularly when the advice goes from one extreme to the other. In contrast to the relative ease of teaching better physical care, parent education in the field of psychologic care has often resulted in dismal confusion. Such failure of the wonderful promise of better mental health due to better psychologic insight seems to be related to the contradictions inherent in different psychologic theories, their simultaneous and often mechanical application, and the neglect of some of the underlying problems.

Deliberately oversimplifying, I shall sketch the background of the various recommendations. Two main schools of thought can be recognized. According to one, children are more or less like blank pieces of paper and it is up to the parents to make the correct entries, or to "condition" a child to the correct way of life. The academic source is the psychologic teaching of behaviorism.

Translated into practice it implies child care in which everything is prescribed in exact terms. This trend was congenial to the thinking of scientific pediatrics. The combination resulted in a system of child care characterized by rigid schedules for feeding, toilet training and every other activity, that is, an over-all atmosphere of emotional sterility. This rigid school was the vogue from 20 to 30 years ago.

The opposed psychologic approach has its main source in psychoanalytic theories. It starts with the assumption that an infant is a bundle of intense emotions and instincts and that he "knows" in a mysterious way everything that is good for his future development. Hence the chief task is to satisfy to the fullest the child's instinctual demands and not to interfere with the unfolding of his drives.

This philosophy has been reinforced from the progressive educational movement. In addition cultural anthropologists came back from the far corners of the earth reporting on the wonderful permissive customs and on the absence of mental disease in some of the primitive tribes. They advised these same customs for child care in our society.

This approach was slow in convincing the pediatricians. However, during the last two decades the star of this modern "permissive" school has been in ascendancy. At present the emotional orientation carries the field. A good deal of its most effective ammunition has come from proving the scientific school of rigid scheduling dead wrong.

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The system of infant care that developed from this orientation advises exceedingly lenient methods in order to avoid frustration and repression. It advocates the lavishing of love and affection upon the child, prolonged breast feeding on self-demand, gradual and late weaning, and late and permissive bowel and bladder training. The emphasis throughout is on a loving relationship between mother and child. The trend has been to introduce this earlier and earlier. The most recent step is the rooming-in movement with the additional emphasis of bringing the father into the loving team.

In spite of the glaring contrasts these two main approaches have many features in common; they both suffer from inconsistencies in their practical application.

Lest I be accused of a nihilistic attitude I wish to make here a declaration of faith: I do believe in the importance of fulfilling the emotional needs of infants and children. I also believe that our present-day knowledge and understanding could be adequate, even though we don't have all the answers, and could be of real help to parents and children if it were used in a way that makes sense.

The following remarks are based mainly on observations, in private practice, of parents and children who have consulted me about a great variety of behavior problems and emotional difficulties during the past 10 years.

In my experience modern parents, in a well-meaning effort at doing right by their children, have tried faithfully to follow the changing fads and fashions of child psychology. I am impressed by the fact that the more anxious and insecure parents are in their basic attitudes the more prone they are to become indoctrinated with psychologic theories. It does not seem to matter much which school they try to follow. Of much greater importance is the basic conviction of such parents that potentially everything they do to or for their children may turn out to be wrong. They are afraid that even the most innocent act or omission on their part may cause some mysterious far-reaching harm in the dim future.

The psychologic experts in their eagerness to give advice seem to have overlooked the fact that to change customs and behavior patterns is not an indifferent procedure but may create new psychologic problems. Many parents have become so self-conscious and confused that they are unable to use their innate judgment and inner resources or to apply effectively any method they are taught. Children raised in such homes are apt to become disturbed on account of this over-all confusion and uncertainty, and not because of the correctness or inadequacy of any one aspect of their training.

Parent education has proceeded on the basis of certain common tacit assumptions. There seems to be a general belief that if one would treat all children alike, if one only knew the "correct" methods, they all would become well-adjusted, nonneurotic human beings. This search for the best method neglects the inherent individual differences which demand treatment in accordance with individual needs.

In human physiology it is customary to speak of the organism in terms of a complicated machinery. This has also been applied to psychologic processes and there is talk of psychologic "technics." While such a concept may be permissible as a figure of speech, it becomes destructive and self-defeating when applied to living children. In contrast to technology or physiology, the application of a psychologic technic involves a human element that is of much greater importance than any inherent merit of the method.

It is easy to teach all mothers how to sterilize bottles or how to give orange juice and vitamins. The result will be more or less uniform. Yet if we tell mothers "You must give your child more love and affection" or "You must never show anger or impatience,"

then this will be put into practice in as many different ways as there are mothers. Such advice is often superfluous, because parents always loved their children as best as they could. It may lead to utterly dishonest situations where a mother may pretend feelings she does not really experience. I have known a girl of five who told her mother one day: "I feel so sorry for you, Mom; you try so hard to love me but you really can't." Another boy of six would cover his ears and run screaming out of the room when he heard the word "love" because he knew something unpleasant was in store for him. Both these children suffered from serious behavior disturbances and were mistrusting and utterly confused about any situation that involved feelings.

In the verbal formulations psychologic teaching has focused almost exclusively on what is called the "child's needs." The rights and needs of parents have been sadly neglected. At best parents are admonished to develop the "right attitude" as if they could change their feelings at will. Most of what is going on in the emotional interplay between people, including parents and children, is more or less outside of awareness. Children respond to these genuine, though often unconscious emotional attitudes of their parents and not to pretended feelings.

I have always been impressed by the stern and authoritarian tone of psychologic advice to parents; it often sounds like talking down to blank-faced automatons. This applies to both the exponents of "rigid training" and "strict schedules" as well as to enthusiastic crusaders for indulgence, permissiveness and good emotional parent-child relationship. If I am not mistaken, the number of "shoulds" and "must nots" for parents increases with the degree to which attention to the child's every need and wish is stressed. If I were facetious I would summarize it as "the more permissive the preaching, the more authoritarian the teaching."

This approach in the current teaching overlooks the root problems of the modern family. Psychologic guidance is not a new-fangled invention that has been introduced into a vacuum. It is intrinsically related to the enormous changes in our social, economic and cultural life and their repercussions on the individual family. These changes are an historical fact. It is the task of the wider community to help parents to counteract disturbances resulting from these changes, instead of blaming them and holding them individually responsible as is done in much of the psychologic writing.

This approach—that everything that happens to a child depends on his parents doing the right or wrong thing—implies an underlying assumption that parents are all-powerful and all-responsible. I see in this concept a real menace for healthy mental development. It overburdens parents with guilt and apprehension. If they have theoretically the power always to do the correct thing and to foresee the future, then they carry also unlimited responsibility for any harm befalling the child.

Parenthood, of course, is and has always been a responsible task and it makes a great deal of difference whether this task is carried out with intelligence and devotion or with neglect, possessive domination or ignorance. I am not talking about the natural responsibility of parents.

The teaching that parents should raise children according to an ivory tower ideal may also have an undermining influence on the child's concept of himself. Fundamentally it implies that a child's development is a monument to his parents' success or failure in being perfect, and not an expression of a child's innate capacity to mature according to and in fulfillment of his individual potentialities.

Personality development takes place as an interplay between a child's inborn needs

and capacities, which includes the capacity for adaptation, and the influence of early emotional and educational experiences. Present psychologic teaching when rigidly applied, with over-direction in certain areas and over-permissive avoidance of guidance in others, may interfere with the development of usefully organized adaptive behavior, that is, it may result in maladjustment and emotional disorder.

Some of the inconsistencies are due to the fact that many psychologic methods are designed to correct errors of the past instead of fostering adaptive behavior so that the child faces life realistically.

An old Prussian story comes to mind. In a certain garrison a fence needed painting. In order to prevent passers-by from touching the wet paint six soldiers were commandeered to walk around the fence. Twenty years later an efficiency-minded new commandant examined the disposition of his men and discovered that six soldiers walked, day and night, around certain barracks. After exhaustive research the original reason was rediscovered. It seems to me that much of what is advocated as newest psychologic technic is akin to the guards pacing around a fence painted 20 years ago.

To recognize something in the past as harmful does not make doing the opposite necessarily good. To be sure, over-stern discipline resulted often in repression and vengeful unhappiness. The cure or prevention for this is not to let children run wild so that they can act out all their impulses and drives. The products of such dabbling in psychology are not happier children but confused and undisciplined brats. The excesses of doing the opposite are particularly apparent in the abuses of a "freer" sexual education.

The correction of isolated errors of the past is not only useless; it may lead to recommendations that are mutually exclusive. To give an example: Mothers are told in great detail what they must do in order to prevent jealousy in an older child, and how they must not neglect to pay special attention to his needs. At the same time they are told that the new baby must not be exposed to any frustration, specifically that he must be fed on self-demand, that is, whenever he cries.

If things go exceptionally well and the mother is a relaxed and disciplined person she may be barely able to fulfill both recommendations. But for many women, worried at every turn that they are doing something wrong, these two demands result in a conflict impossible of solution. Her children will react with anxiety to her uncertainty and tension and will make more demands on her. It would be much more sensible and psychologically healthier to give such a mother a definite but flexible feeding schedule for the baby and to help her to be more natural with the older child and to let him share in the joy about the new member of the family instead of excluding him in order to prevent jealousy.

This is but one example of the many inconsistencies that can be easily demonstrated in the current psychlogic teaching. It seems to me that we have asked the wrong questions, or have formulated them inaccurately. The emphasis has been on what a child needs, when he needs it and why. Little attention has been paid to the problem of how a mother carries it out and of what it means to her in particular when the advice is alien to her own experiences or even runs contrary to her fundamental feelings of what she thinks is right.

There has been much talk about the importance of a satisfactory mother-child relationship, that means "satisfactory" for both partners, the child as well as the mother. Psychologic child care should be approached with the question of how an individual mother can fulfill her child's demands and also consider her own justified needs.

Only a mother who is emotionally at ease, not overtired and anxious, can make her

child feel comfortable. There is no prescription counter "security" for children. The infant derives this feeling from the emotional atmosphere around him. If a mother feels abused by impossible demands and is over-anxious in handling the baby she will convey the uneasiness of her attitude regardless of whatever lenient technic she uses.

The pediatrician finds himself in the crucial position of giving emotional support to young parents, not by lecturing them on child psychology, but by advising them about child care that is most appropriate to their individual personalities, idiosyncrasies and fears. He must be free from dogmatic convictions that there are standardized technics that would be correct for any and every child. There simply is no absolute "right" way in which a hypothetic child could be manipulated into becoming a perfect adult.

Young people of today enter parenthood without much knowledge about children. This factor of ignorance must be handled realistically. It is good preventive mental hygiene to tell parents ahead of time what to expect in their child, to give detailed instructions about the physiologic care and to encourage them to ask questions when they are in doubt.

It is the pediatrician's job to be informed about the changing trends in child psychology, to understand their presumed meaning and goal so that he can apply them according to the individual needs of his patients. He must protect parents against what Brenneman called the menace of psychiatry, against impossible emotional demands and the psychologic double-talk that "Heaven will fall if you do and earth comes to an end if you don't."

Reference

1. Bruch, Hulda, Don't Be Afraid of Your Child: Guide for Perplexed Parents, New York, Farrar, Straus & Young, 1952.

Spanish Abstract

Aspectos Psiquiátricos Derivados de los Cambios en los Métodos Educativos del Niño

El artículo llama la atención acerca de los problemas que han provocado los cambios deliverados en los métodos de educación del niño particularmente cuando los que se aconsejan van de un extremo al otro. Contrariamente a la relativa facilidad para enseñar el mejor cuidado físico del niño, la educación de los padres en el campo de la atención psicológica a menudo ha resultado en una confusión funesta. Este fracaso de las promesas maravillosas de una mejor higiene mental consecuencia de un mejor y profundo conocimiento psicológico parece estar relacionado con las contradicciones inherentes en teorías psicológicas diferentes, en su aplicación simultánea, a menudo mecánica y el olvido de algunos de los problemas fundamentales.

Simplificando, se han reconocido dos escuelas de pensamiento, la una, en que se considera al niño poco mas o menos como hojas de papel en blanco y son los padres quienes deben hacer las "entradas correctas" o "condicionar" al niño a la forma correcta de vida. Su fuente académica es la enseñanza psicológica del conductismo. Traducido a la práctica implica que el cuidado del niño debe prescribirse en terminos exactos en todo y esta tendencia se identifico con el pensar de la pediatría científica. Su combinación resulto en un sistema de atención del niño caracterizado por horarios rígidos de alimentación, de adiestramiento de los esfinteres y de toda actividad, es decir, una atmósfera de esterilidad emocional por completo. Esta escuela estuvo en voga hace veinte o treinta años.

El acercamiento psicológico opuesto tiene su fuente principal en las teorías psicoanalíticas. Comienza por asumir que el niño es un conjunto de fuertes emociones e instintos y que conoce, en forma misteriosa, todo aquello que es bueno para su desarrollo futuro. Por lo tanto, la tarea principal es satisfacer al máximo sus demandas instintivas y no interferir con el desenvolvimiento de sus tendencias. Esta filosofía ha sido reforzada por el movimiento de la educación progresiva.

Además, los antropólogos roportan las maravillosas costumbres tolerantes, y la ausencia de enfermedades mentales, en algunas tribus primitivas, aconsejando las miasmas costumbres para el cuidado del niño en nuestra sociedad actual.

Este acercamiento hacia el niño fué lento en convencer a los pediatras, sin embargo, durante

las últimas dos décadas esta escuela ha alcanzado ascendencia. En el presente la orientación emocional tiene la palabra y una bueno parte de sus armas mas efectivas han salido de probar que la escuela científica de los sistemas o métodos estrictos está plenamente equivocada.

El método de educación del niño que se desarrolló de esta orientación aconseja procedimientos excesivamente tolerantes con objeto de evitar fustraciones y represiones. Adboca el amor y el afecto en forma pródiga, autodemanda en la alimentación materna que debe prolongarse, destete gradual y tardío y adiestramiento tardío y tolerante de los esfínteres. El énfasis en todo son las relaciones cariñosas entre madre e hijo y la tendencia ha sido de intruducir dicho contacto cada vez mas temprano.

A pesar de los claros contrastes, estos dos métodos principales de acercamiento al niño tienen muchas cosas en común pues ambas sufren de inconsistencias en su aplicación práctica.

Después de estas consideraciones el autor del artículo hace una declaración de fé afirmando que cree en la importancia de llenar las necesidades emocionales del niño y afirma que lo que sabe y entiende de él en la actualidad, aun cuando no se tiene una respuesta a todo, sería adecuado y de ayuda real para los padres y los niños si se usa en forma que tenga sentido.

A continuación el autor llama la atención sobre algunas de sus observaciones, hechas durante el ejercicio privado de su profesión en padres y niños que lo han consultado acerca de una gran variedad de problemas de conducta y dificultades emocionales, en los últimos diez años.

Los padres ansiosos e inseguros facilmente se doctrinan con teorías psicológicas pero lo que es mas importante, es su convicción básica de que potencialmente cualquier cosa que hagan por sus niños pueda estar equivocada a la larga y causarles algun daño en el futuro.

Los expertos en psicología, en su ansiedad para dar consejos han despreciado el hecho de que el cambiar costumbres y patrones de conducta no es un procedimiento indiferente sino que puede crear nuevos problemas psicológicos confundiendo y haciendo temerosos a los padres hasta imposibilitarlos para usar su juicio innato y recursos propios o aplicar con efectividad cualquier método que se les haya enseñado. Los niños educados en tal ambiente estan confusos igualmente.

En la busqueda de los métodos mejores para tratar al niño en general se han olvidado las diferencias individuales inherentes las cuales demandan tratamiento de acuerdo con las necesidades particulares.

Al recomendar a un padre ciertas formas de resolver una situación psicológica, sea el caso: "debe usted dar a su hijo mas cariño y afecto" esto se pondra en práctica en tantas formas distintas como madres existen y los resultados pueden ser contraproducentes.

También se han olvidado los derechos y necesidades de los padres, exigiendoles que cambien sus sentimientos, y los niños responden a menudo a las actitudes emocionales inconcientes de sus padres y no a los sentimientos que pretenden demostrar.

Ambas escuelas psicológicas tienen demasiados "debe" y "no debe" hacerse para los padres y coloca en los mismos una responsabilidad ilimitada cargándolos de culpabilidad y prejuicios.

En realidad se olvidan cuales son los problemas básicos de la familia moderna que estan intrínsicamente relacionados con los grandes cambios sociales, económicos y culturales y debe de ayudarse a los padres a contrarrestar los trastornos que han resultado de estos cambios en lugar de culparlos y señalarlos individualmente como los responsables.

El educar a los niños con el ideal de la torre de marfil puede minar el concepto que tiene el niño de si mismo.

El desarrollo de la personalidad es el resultado de la necesidad y capacidad innatas del niño y la influencia de su experiencia emocional y educativa en su vida temprana. Si en ciertos aspectos se aplica la escuela psicológica indulgente y en otros la rígida se obstrucciona el desarrollo de la capacidad bien organizada de adaptación del niño.

El pediatra se encuentra en una posición crucial para brindar un respaldo emocional a los padres, no dándoles conferencias de psicología infantil sino aconsejándolos de acuerdo con su personalidad, idiosincrasia y temores, la educación del niño que sea la mas apropiada. Debe librarse de las convicciones dogmáticas acerca de técnicas standards que serían correctas para todos y cada niño en particular, pues simplemente no hay un procedimiento absolutamente seguro en que un niño hipotético pudiera ser educado y hacerlo un adulto perfecto. Ens obligación del pediatra estar informado acerca de la tendencia en los cambios de la psicología infantil para entender su significación y meta, de manera que pueda aplicarlos de acuerdo con las necesidades individuales de sus pacientes.

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PSYCHOSOMATIC STUDY OF INFANTILE ECZEMA

I. Mother-Child Relationship

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IF WE are to believe that the only important etiologic factor in infantile eczema is an allergic one, we would leave unexplained many clinical phenomena connected with the disease. It is quite possible that other factors besides the allergic ones play important roles and that if these could be identified and taken into account the doctor would be able to understand better the many puzzling features of the course, prognosis and therapy of this disease. This paper is submitted as a contribution to the study of nonallergic factors in the cause and course of infantile eczema.

PRELIMINARY ETIOLOGIC CONSIDERATIONS

The primary thesis of this paper is that eczema arises in certain predisposed infants because they fail to obtain from their mother or mother-substitute adequate soothing physical contact (caressing and cuddling). The paper will be concerned primarily with an investigation designed to test the validity of this hypothesis.

In a group of infants 6 to 12 months of age studied by Spitz,[1] it was noted without further comment that the incidence of eczema was quite high. These infants all had the following history in common: they had been separated from their mothers and were being raised in a foundling home. For most of the infants this change must have necessitated a great diminution in the amount of attention, including physical contact, which they received from mother-substitutes. In a recent paper devoted to a study specifically of infants with eczema, Spitz observed that the mothers of these infants gave them little physical contact.[2] Knowledge of the latter paper was not available at the time this study was undertaken. As we shall see, the writer's findings confirm those of Spitz.

In a few cases coming to the writer's attention before the present study was begun, the hypothesis seemed helpful in explaining the clinical course of eczemas. One case is summarized here:

CASE A

N. H. was a spastic child referred to the Institute for Juvenile Research at the age of 6 yr. in order to determine whether she was a suitable candidate for protracted specialized education. When she was 3 mo. of age she developed such a severe case of eczema that she had to be hospitalized. During this period the family lived with the maternal grandparents. Frequent quarrels ensued between the mother and other members of the household over the mother's insistence that no one handle the baby but herself, and because she believed that if the baby were crying and no obvious reason for the crying were found, the baby should be allowed to cry without being handled in any way. In the hospital the eczema cleared up in about 10 days, but before the child could be discharged she developed an illness with high fever and convulsions, so the hospitalization, with only a short interruption, was continued for 2 mo. It was following this illness that spasticity and

From the Institute for Juvenile Research, Chicago.

Case material contacted at the Pediatric Out-patient Departments of the University of Illinois and Cook County Hospitals.

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athetosis made their appearance. This time when the child was sent home, she was a "sickly, delicate" child and she received much more handling than she had ever previously received. No more was the "let her cry it out" policy followed. The eczema never returned as it so often does after an intercurrent illness has cleared up.

Presumably being held by a mother has value of an emotional kind for the infant. However, the writer has reason to believe that the physical contact provided even inadvertently by the mother in holding an infant may have value in addition of a more purely physiologic nature. One can say that it is important for many infants to receive pleasant skin sensations (tactile, thermal, pressure) in this way and it is the writer's hypothesis that lack of these pleasant sensations, in certain infants, contributes very significantly to the development of a particular type of pathology in the skin, eczema. This particular interpretation of the findings (i.e., the stress on physiology) is based on certain considerations relevant to the pathophysiology of the condition and will be discussed in a subsequent paper.

All parents know that fretful babies can often be made quiet and contented by simply picking them up and acting reassuringly. Often they feel (as did many of the mothers seen by the writer) that the babies frequently cry for the sole purpose of being held. An infant may, of course, cry for a variety of reasons. However, regardless of the precise reason, we may assume that ordinarily the crying represents both an expression of the infant's discomfort as well as a plea to the mother to alleviate this discomfort. Thus, when the child's crying is frequently unheeded there is good reason to believe that the child is receiving inadequate caressing. Furthermore, when the mother habitually does nothing for the child even when it cries, it seems likely that she is reluctant or unable to hold it at other times. It occurred to the writer that data on unheeded crying could very well serve as an index of the amount of caressing given to the child. Accordingly, obtaining information on this point was made the goal of this investigation.

Commonly, one would expect that inadequate caressing would be present as a result of deficiencies in the routine handling of the infant. However, it could also come about under special circumstances such as weaning, illness of the mother or child, weakness of the mother, physical separation of mother and child, or the birth of a sibling. Acute changes should be evident within a few weeks, at most, following an event leading to diminished maternal handling. This is in accordance with the observation of Sulzberger[3] and others that it takes from 24 to 48 hours for eczematous lesions to reach their full clinical development when produced by an isolated contact with a known allergen.

A few words of caution are in order before proceeding to consider the theory further. Infants show marked differences in behavior apparently because of constitutional differences.[4-6] This implies that their needs are different and that, as concerns maternal handling, some may need relatively a great deal, whereas others may be satisfied with comparatively little. What is neglect for one infant may be adequate for another. It is impossible to impose absolute standards as optimal or minimal adequate maternal handling of infants.

Again, the hypothesis offered would not attempt to deny the existence of eczema beginning obviously because of local irritation (such as irritating discharges from the mucous membranes); or from clearcut food allergies, etc. However, the suggestion is made that in all these cases, and particularly in those where allergic factors seem to be important, psychogenic factors may be playing at least a crucial aggravating role.

Methods of Investigation

It seemed to the writer that the thesis that the child with eczema might have received inadequate caressing by the mother could be tested on the basis of material obtained by interviewing the mother.

The procedure was as follows:

Twenty-five mothers whose children under the age of 2 yrs. were suffering from eczema were interviewed by the writer. They were contacted at the Pediatric Out-patient Department of the Research and Educational Hospital and the Children's Dermatology Department of the Cook County Hospital in Chicago. The mothers had gone to these clinics with their children to obtain therapy for their babies' skin condition, but had no idea that when they got there they would be asked a number of questions about the emotional climate of the home. The group was entirely unselected except for the requirement of a diagnosis of eczema by a competent pediatrician or dermatologist. None of the mothers who were approached by the writer refused to grant an interview.

The interview itself usually lasted about 20 min. and began with an explanation by the writer that he was not seeing the mother for the purpose of helping her with the child's skin trouble, but that another doctor would do that. Also, he made it clear that he understood that it was to obtain such help that the mother had come to the clinic in the first place. He then said he would like to ask the mother questions pertaining to any problem she might be having regarding the care of the child. The individualized portion of the interview began with the writer's asking several general and innocuous questions. Thus, the mother was usually asked how many children she had, and some questions about her health in pregnancy and immediately afterwards. Soon she was asked the following question and the answer to it provided the crucial data: "Different mothers have different ways of handling their children and I want you to tell me which way you handle yours. When the baby cries do you believe it is best to let it alone, or do you believe that it should be picked up?" An attempt was made in every instance to learn the answer to this question regarding the premorbid period.

Not infrequently during the interview the mother would give some incidental information or speak in such a way as to make it seem unlikely that her direct answer to the crucial question was actually correct. For this reason in every case the interview was continued beyond this point. The interviewer would then get further information concerning the mother's emotional state and the family interrelationships and only after the interview was over would it be evaluated.

The replies were rated in the following manner. If the mother indicated that it was common even though not necessarily usual to let the baby cry it out, it was felt that the baby did not receive adequate caressing by the mother and it was accordingly scored as a minus (—). If the eczema appeared shortly after a sudden diminution in the amount of maternal handling of the child, the case was rated as a minus regardless of the reply.* If the mother indicated that she almost always picked up the baby as soon as it cried, it was felt that this baby did receive adequate caressing and this was scored as a plus (+).

There were a number of replies obtained that could not be clearly classified as either positive or negative and this group was classified as plus-minus (±). Sometimes mothers would say they deliberately let the infants cry a little but not too long. If, on being questioned closely, they said they never let the infant cry more than 10 minutes, this case, too, would be included in the plus-minus group.

While plus-minus classifications were common, they were not so common as to prohibit an adequate diversified statistical tabulation of cases. It was the writer's opinion that most of the plus-minus cases should have been classified as negative and that most psychiatrists would have so regarded them. However, such a handling of the data would have been subject to the understandable criticism that the examiner might have been prejudiced in his findings and so the evaluating system just outlined was followed.

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* This criterion decisively influenced the rating of but one case (Case 17), changing the rating of ± to —.

The ratings were made by 3 colleagues of the writer to whom the case histories were read. In reading the histories to the raters the nature of the presenting problem was not revealed so that those rating them were not able to distinguish the eczema cases from the controls. A high degree of agreement on the ratings of the individual cases was found among the raters themselves, and between the consensus of their ratings and those made independently by the writer.

Now it was recognized that despite these precautions (or perhaps because of them) the charge could still be made that the examiner might have influenced the results unduly. An attempt was made to meet this objection by rating the data on the basis of the immediate answers to the questions regarding the mother's handling of the crying baby. Such answers could hardly have been influenced by the examiner's bias. These statistics were then compared with those obtained on the basis of evaluations of the complete interview in order to see how influential theortically this subjective factor could have been.

The following objections to the method were known by the writer, but were felt to be unavoidable. First, that the information obtained in a single brief interview might not be reliable. However, it was hoped that by emphasizing not the absolute findings, but rather the comparison of findings in an eczematous with those from a control group, this factor could be minimized.

Second, the assumption might not be true that if the mother picked up the infant when it cried, it got adequate caressing. Some mothers might seldom pick up their infants unless they cried. Again, some mothers might pick up their babies often enough, but without making the skin contact pleasant. Nevertheless, on the basis of the ratings made in this study they would be credited with a plus-rating making it seem as if they were providing their infants with adequate skin contact. On the other hand, in the majority of cases where mothers frequently did not pick up their babies when they cried, the material related in the interviews revealed that they probably picked the babies up relatively little even when the babies did not cry; so that the minus-ratings were considered fairly reliable indicators of inadequate caressing.

A control group of 18 mothers from the same clinic was obtained. The interviews with these mothers were conducted in exactly the same fashion as in the group studied. The criteria for controls were that the infant should be more than 6 mo. and not more than 24 mo. of age and that there should be no history of its having had any rash which might have been eczematous. Further, it was thought preferable, in order to sharpen the statistics, to avoid children who were brought into the hospital because of a complaint which quite likely had a prominent psychogenic background. Thus, the children used in the control group were mainly well babies, and babies brought in because of infections or congenital defects.

Results

The results of findings in these 25 cases of infants with eczema and the 18 controls are summarized in table 1.*

TABLE 1

Percentile Findings

	+	±	−
Eczema	12	28	60
Control	66.6	16.6	16.6

TABLE 2

Percentile Findings Based on Early Responses

	+	±	−
Eczema	24	20	56
Control	61	11	28

* The results were found to be statistically significant according to the chi-square test by Mr. Irving Leiden, staff psychologist at the Institute for Juvenile Research.

In order to overcome the objection that the examiner may have influenced the mothers' answers unduly, the interviews were scored on the basis of the mothers' earliest responses at a time the examiner's influence must have been minimal. The results of this scoring are listed in table 2.

Discussion of Findings

1. On the Validity of the Thesis: Inspection of the preceding tables indicates that there is a distinct difference in maternal practices among the mothers of eczematous infants and the mothers in the control group. Comparisons of the scoring of interviews where the material was evaluated early with those where evaluations were made late reveal no significant statistical difference. On a statistical basis then, it was found that eczematous babies were not picked up by their mothers when they cried as much as were the noneczematous infants.

In about two-thirds of the cases the data were very clear on this point. Interestingly, the statistics for the eczema and control groups were almost reversed on the point which was scored. Unfortunately, the statistical series is not large. However, it meets the usual chi-square standards of reliability for such material, i.e., less than one chance in 20 that the findings are accidental. (See also section 3 below.)

Case 26, one of the controls, is typical of the cases which received a plus rating.

Case 26

Patient was 9 mo. of age when seen. The symptom which prompted the mother to seek help for the child was a swelling of the jaws which developed when he was 5 mo. old. Mother never worked and was never separated from the baby. The child was described as a good baby. When he cried, there was a reason. Mother never had to let the baby cry it out. Mother's health was good. However, she was often tired at the end of the day. This was attributed to her having to carry around a baby who then weighed 11.3 kg. Mother had some difficulty with the father because he gambled a great deal. Her most serious marital problem, she felt, arose from the fact that she was a Catholic and the father, Protestant. At the present time the apartment is shared with another family.

This case illustrates that although a mother may not find herself in an ideal situation, she need not necessarily fail to provide her child with adequate physical contact.

The following case, Case 8, stands as a clear contrast to Case 26. It is typical of the cases which received a minus rating.

Case 8

Patient was 16 mo. of age when seen. The rash had begun at 3 mo. of age. Mother's health and strength had been good since the birth of the child. The patient had been easy to care for and had never been a feeding problem. Three families and a grandmother share the apartment. Grandmother cares for the baby when mother is out of the home. When patient cries and is not hungry, if there is nothing (obviously) wrong with her, mother lets her cry. If she didn't, she might spoil the child. Mother was separated from the child only during her hospitalization in connection with the birth of a younger sibling. The parents quarrel a great deal, making mutual accusations of infidelity. This makes mother nervous and she admitted that she was unnecessarily irritable and punitive with the child.

Thus far, we have seen from the tables that, as a group, the eczematous babies received less physical contact with their mothers than did the noneczematous group.

A two-thirds majority of the eczematous infants were found by these standards to have had too little caressing and cuddling. What about the other one-third of the cases in the group, which, after all, is a sizeable minority? Two-thirds of this minority group were rated as ±. Further study of this group can contribute little here. However, a more

detailed examination of the small remainder of cases which received plus ratings will be instructive.

There were three such cases. Under detailed analysis they show strong possibilities that, in fact, these infants did not receive adequate caressing. The case histories follow.

CASE 9

Patient was operated on for pyloric stenosis at 2 wk. of age and came home from the hospital at 8 wk. The rash appeared almost immediately at this time. Mother was upset by the infant's operation and thinks she is still "run-down" as a result of this upset. The parents were separated while mother was pregnant with this baby and mother tried to make up to the child for its lack of a father. Recently she took the child with her and visited father who lives in another town. During the 3 wk. of their stay there the baby's eczema improved markedly. Mother admits that she often gets irritated with the baby and spanks it. However, she insists that she always picks it up when it cries. She feels that a baby will not cry unless there is a reason for it. For example, it may merely need cuddling. However, when she was asked about her handling of the infant when it cries, she made the significant slip of the tongue, "Well, I let him—I always pick him up." Later she admitted that she is often half-hearted about picking up the baby. The mother was a well-educated and intelligent woman although of a low-income group. She had read many books on child care and could quote almost verbatim from them. Thus she knew all the "approved" methods. The baby is still a poor feeder although its vomiting has improved. He also suffers from asthma.

Comment: Mother did not impress the examiner as being a warm person. Her handling of the baby seemed largely mechanical. Actually she openly admitted having many hostile feelings toward the child. One may suppose that losing her husband while pregnant made the child less welcome to this youthful and attractive woman, and that this experience might have contributed significantly to causing such hostile feelings. If this is so, it would support the impression of a poor mother-child relationship. Mother's slip of the tongue raises the possibility that she was untruthful in saying that she picks the baby up whenever it cries. At least it suggests reluctance to hold the child. One is tempted to conclude that even if mother does indeed pick the child up as much as she claims, the skin contact which she offers the child is not soothing and thus does not meet the infant's needs. Here for the first time we are confronted with an important defect of our investigative method: it yields information bearing only on the quantity and not on the quality of the skin contact.

CASE 21

While this mother seemed to have warmth for her child, there was a possibility that all was not well in the mother-child relationship in that the baby vomited a great deal and was often constipated. Postpartum the mother developed a pelvic inflammatory disorder and had to return to the hospital frequently for check-ups. Since then she gets tired easily and suffers from backaches.

Comment: Possibly mother's poor health interferes with her giving the baby sufficient cuddling. On the basis of the information obtained it would seem that this mother was the most adequate of the 3 discussed here.

CASE 24

The baby was an illegitimate child. Father backed out of his promise to marry mother when she was pregnant. The infant was breast-fed entirely until he was 2 mo. of age. At that time the mother cut down her nursing abruptly to one nightly feeding and gave evaporated milk for the other feedings. The rash developed 2 wk. after she made this change. However, mother had told a pediatrician on an earlier date that the rash had developed when the infant was 8 wk. of age. Mother stated that when she bottle-fed the baby she usually held him. There are several relatives in the home who help to care for the baby. Mother picks him up rather reluctantly as soon as he cries. She does this mainly because the crying irritates the maternal grandmother and she does not want the latter to nag her to pick up the baby. She told with bitterness how the baby would fall asleep in her arms and reawaken the minute it was placed in bed. Mother was somewhat concerned but on the whole rather fatalistic about the baby's getting spoiled. While she had some warmth for the child, she was a rather immature person and angry about the situation into which the baby had thrust her.

Comment: The rash began 2 wk. after the sudden diminution in breast feeding. It was decided to classify this case as though this factor were unimportant because 2 wk. is perhaps slightly in excess of the period in which one might expect the eczema to develop if it developed as a consequence of a single event. Obviously, however, the chronology of events as given might not be precisely correct. The interval might have been shorter. A further reason for deciding to discount the effect of the weaning in scoring the case was that the mother claimed she held the baby when she bottle-fed it. Certainly, however, one could suppose that this mother, as in Case 9, was hardly able to give this baby much really soothing physical contact because of the great anger she must have felt toward it.

Scrutiny of these three cases of eczematous infants which were rated as having received adequate skin caressing makes one skeptical that this was actually the case. As was suggested above, then, these three cases are not even exceptions which prove the rule. They seem to point to an inadequacy of the methods of rating rather than to a fault of the theory.

One might ask if possibly the changed handling of the infant did not follow rather than precede the development of the rash. It is plausible that the development of a rash would make an infant appear repugnant to the mother or too demanding of her time and that for such reasons she might leave it alone. There was good evidence, however, that such explanations were incorrect. In several cases it was possible to show definitely that the inadequate handling of the infant had preceded rather than followed the onset of the rash. The following case illustrates this point.

CASE 2

The rash appeared when the infant was 5 mo. of age. The girl was the 8th child in the family and, according to the mother, was not harder to care for than the other children. But mother "had so many that it just got on my nerves, that's all." At first an older daughter and mother's mother helped a great deal in caring for the child. Mother explained that since her nerves were bad she couldn't be bothered much with the child and grandmother could take better care of the baby than she. Mother attributed her nervousness to difficulties in raising the large family and to severe quarrels with her husband who drank and went out with other women. The rash appeared when the mother decided to change the practices in caring for the child. "Up until the fifth month the baby got real good attention, then I began letting her cry a little bit." Grandmother always liked to pick the baby up when it fretted but after the 5th mo. when mother often let the baby cry it out, mother would insist that the child be let alone.

2. Causes for Inadequate Caressing of Infants: The reasons which the mothers gave for not picking up the baby when it cried varied. Most common was the rationalization that the mother did not want to spoil the infant. Actually, one found that the mothers in such cases were generally unhappy over being saddled with the work and responsibility of caring for their children. This was often but one aspect of their dissatisfaction with their marriage (in some cases with their lack of one) or with mature responsibilities of any kind. Thus, providing themselves with a justification for neglecting their children allowed these mothers to indulge with less guilt the conscious or unconscious wish that they not be tied down or overburdened with inescapable responsibilities—in effect, that they not have children. Most revealing was the frequent history (as in Cases A, 2 and 16) of quarrels between the mother and other members of the family because they would not let the baby alone. It was usually clear that this attitude was present from the time the infant was born. In a few cases the mothers indicated that they were too weak to give the infant all the attention which they felt it should have had.

On the other hand, there were often curious reasons which the mothers in the control group gave for picking up the infant. (In some cases these, too, may have been rationali-

zations.) For example, a few of them said they were afraid to let the baby cry because it would disturb other occupants of the apartment. Others were afraid to let the baby cry lest he rupture himself. Others felt that the crying might make the baby sick.

Many of these mothers were apologetic about "spoiling" their children. One sensed that such mothers often went on expressing freely their affection for their children despite real or imagined disapproval of their mothering by relatives, neighbors, or doctors. On the other hand, such demonstrations of affection probably were at times excessive. This study suggests, however, that unless the unwholesome aspect of the mother's handling of the child was manifested as not providing the child with adequate caressing, the consequence was something other than eczema.

In any event, the present investigation demonstrated quite clearly that the mother's insufficient handling of the eczematous child was usually the result of an attitude on her part, and it was often possible to show that this attitude had preceded the appearance of the rash.

3. Etiological Significance of Lack of Physical Contact: As we have seen, the present findings and those of an independent observer (Spitz[2]) demonstrate an association between lack of physical contact and infantile eczema. We shall examine now the reasons for believing that the lack of physical contact plays an important role in causing the eczema.

In the first place, in almost every case which received a minus rating it was at least very probable (as in Case 2) that the insufficient picking up of the child had preceded the eczema. In only a very few cases did it seem at all possible that the maternal practice might have begun after the eczema appeared. As a matter of fact, in most cases it seemed that the child got more not less contact after the rash appeared.

Secondly, in several cases such as Case 2 the eczema followed rather quickly an abrupt lessening of soothing physical contact given the infant. Causes of this included weaning, hospitalization of mother, and loss of a helper.

Further evidence for the validity of the hypothesis would come from demonstrating an improvement in the eczematous state when more soothing physical contact was made available than previously. The selection of the case material in this study largely precluded cases of healed eczema so that it was not expected to disclose cases of this sort. However, Case A, cited above and the following case, Case 1, seem to illustrate the therapeutic benefit of soothing physical contact.

CASE 1

The rash first appeared when the infant was 13 mo. of age. During this period the child had been placed in the care of the maternal grandmother and mother would see it about only 3 times a week. Around the time the rash appeared the maternal grandmother became ill and finally mother had to stop working in order to take the baby from her. Mother commented that grandmother did not spoil the child. When he cried in bed the latter would merely give him a bottle. On the other hand, mother would pick him up. Mother admitted that she spoiled him. The eczema improved as soon as the mother took him home with her.

These meagre data are, of course, insufficient to prove that increasing the soothing physical contacts for the infant helped the eczema. However, at this point it is pertinent to cite the findings of Williams[7] in a larger series of cases where changing the mothers' attitudes toward their babies had such beneficial therapeutic results. Williams made a special effort to get these mothers to fondle and caress their babies more than they had done previously. It is probable that in most instances changing the attitudes of

the mothers is a prerequisite to their giving their babies more soothing physical contact.

These findings suggest the hypothesis that lack of soothing physical contact between mother and child is a causative factor in infantile eczema. There is some evidence, but of an inconclusive sort, which suggests that infantile eczema will not occur if an infant does receive adequate physical contact (qualitatively as well as quantitatively) from the mother or mother-substitute.

On the other hand, the findings in this study do not preclude the importance of other factors in the causation of the condition. This study offers no explanation for the lack of eczema among infants in the control group who apparently also had insufficient maternal contact. This may mean that even if the lack of contact were a crucial factor requisite for the genesis of infantile eczema it would not be the only crucial factor. Other crucial factors may include certain constitutional factors as, for example, an allergic diathesis. However, to be sure, it is conceivable also that the hypothesis or the manner of collecting data in the present study is inadequate and that an improved (more specific) hypothesis or more accurate data might differentiate the maternal practices of the mothers of the eczematous babies from those of the entire control group. Certainly, an obvious defect of the present study is the failure to differentiate qualitatively among the types of skin contacts offered the infants by their mothers.

The series of cases studied was not large and the case material was selective socio-economically. These considerations naturally make the author cautious about drawing conclusions from the study. It certainly points up the desirability of checking the findings with a larger and more varied social sampling. Three facts, however, seem to the writer to make the findings and conclusions of this study more significant: (1) they tended to verify a hypothesis derived from a consideration of the incidental findings of other investigators; (2) they were in agreement with the findings of an independent investigator; and (3) the hypothesis seemed very helpful in explaining the onset and course of a number of cases studied in detail.

Therapeutic Implications

The findings in this study suggest that the course of a case of infantile eczema may be largely dependent upon the status of the mother-child relationship. Success and failure of many standard medical regimens may have been largely determined by this factor. The fact that the factor may have been overlooked by the physician did not mean that it was not affected by the entrance of the doctor into the situation. The findings of Williams substantiate a notion which might have been derived from the study, i.e., that failure to change the mother's attitude toward her child is perhaps one of the principal causes of failure in the therapy of the disease.

In attempting to alter the mother's attitude toward the child, the suggestions given by Williams would seem to be generally helpful. The writer would offer the following suggestions merely as a supplement to them.

Mothers should be relieved of fear that the child might be spoiled by giving it too much attention during the first nine months of life. The fact is that infants who are given insufficient attention in this period are apt to be more troublesome both then and later on. Recent findings[8] suggest that eczematous conditions may be aggravated by crying. This is a more concrete argument for not letting the baby "cry it out."

Sympathy and understanding should be offered these women who feel the burdens of motherhood almost too great to bear. At times they may have wished to be free

from such responsibilities, or been angry at their husband or other relations for being critical instead of offering to share the responsibilities in a more constructive manner. Such reactions should be appreciated as logical outcomes of their feelings in the matter. Getting another person to help with the housework, if feasible, should be suggested for those mothers whose relative neglect of their children seems to be a consequence of overwork or poor physical condition.

A sympathetic, confidence-inspiring attitude on the part of the physician may go a long way in making these mothers feel that motherhood is something other than a frustrating, thankless, onerous experience. If a mother is found to be unhappy because of long-standing, deep-seated personality problems, or because of complicated marital difficulties, referral to a psychiatrist or social agency should be considered.

It would be a mistake to interpret the findings of the study in too mechanical a way. One cannot neglect the factor of the mother's attitude. If a mother does not feel affectionate towards her child, the physical contact she might offer it in methodically and mechanically caressing it would probably be more harmful than helpful.

This suggestion, based as it is on the conception of the importance of the quality of the mother-child physical contacts, is derived from considerations which are admittedly beyond the scope of this paper. It is included here for practical purposes and in the hope that it may prevent an over-hasty rejection of the hypothesis of the paper because of possible apparent failures of the hypothesis to withstand a therapeutic test, in certain cases. To clarify any possible misunderstanding the writer wishes to point out that the phrase "inadequate soothing physical contact" in the wording of the hypothesis is intended to convey the notions of both quantitative insufficiency as well as qualitative unsuitability of contact (due probably to contacts of too rough a nature to be soothing). In this study, however, only the quantitative aspects were objectively evaluated. With this scientific "indiscretion" already committed, the writer would like to suggest also that the physician take pains to explain to the mother that all her handling of the infant, as in cleansing it, should be gentle, even when noneczematous areas of the skin are involved; and that under no circumstances should the baby be spanked or slapped so long as the eczema persists. Should a mother become aware that she has become too impatient or too angry at the child to treat it in the tender way indicated, it would seem best for her to entrust the care of the child to someone who can give it this type of care until either the eczema or the mother's attitude has improved.

It would seem best to encourage physical contact mainly by cuddling and gentle patting. Only noneczematous areas should be caressed as even the gentlest caressing of eczematous areas may stimulate pain receptors. Aside from the above precautions, physical contacts should generally be encouraged along the line of using them to make a mother feel more pleased, more at ease, more adequate, and ultimately more appreciated in her role as mother.

Summary

Comparisons of findings in interviews with the mothers of 25 infants with infantile eczema and of 18 control cases revealed that in a significantly higher proportion among the eczema cases the mother tended to let the baby cry without picking it up unless there was some obvious physical discomfort present in the infant. This was taken to indicate that most eczematous infants received inadequate caressing and cuddling. (Spitz, in an independent investigation, came to a similar conclusion.) While the study was de-

signed to test the possibility of a quantitative lack of maternal-child physical contact (which was demonstrated), the study did not rule out the possibility that qualitative aspects of the contacts were also significant.

The lack of cuddling and caressing of the child was found to result most commonly from an attitude on the part of the mother of wishing to be free from being burdened with the care and responsibility of raising a child. These mothers would generally try to justify their infant-rearing practices by saying that they did not wish "to spoil" their babies. In a smaller group of mothers it seemed likely that their relative lack of caressing was due to physical fatigue or weakness.

The lack of cuddling and caressing in most of the cases studied was felt to be an important factor in causing the eczema. However, other factors such as constitutional predisposition and allergy were possibly equally important. Certain therapeutic suggestions were made on the basis of the hypothesis.

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References

1. Spitz, R., Anaclitic depression, in Psychoanalytic Study of Child, New York, International Universities Press, 1947, vol. 2, p. 313.
2. Spitz, R., in Panel Discussion on Psychosomatic Problems, Bull. Am. Psychoanalyt. A. **7**:244, 1951.
3. Sulzberger, M. B., Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 63.
4. Fries, M. E., Psychosomatic relationships between mother and infant, Psychosom. Med. **6**:159, 1944.
5. Bergman, P., and Escalona, S., Unusual sensitivities in very young children, Psychoanal. Study of the Child, New York, International Universities Press, 1949, vol. 3-4, p. 333.
6. Aldrich, C. A., and Aldrich, M. M., Babies are Human Beings, New York, The Macmillan Company, 1938, chap. 5.
7. Williams, D. H., Management of atopic dermatitis in children: Control of maternal rejection factor, Arch. Dermat. & Syph. **63**:545, 1951.
8. Kepecs, J. C., Robin, M., and Brunner, M. J., Relationship between certain emotional states and exudation into skin, Psychosom. Med. **13**:10, 1951.

Spanish Abstract

Un Estudio Psicosomático del Eczema Infantil

Partiendo del punto de vista de que si se considera el factor alérgico como el único factor etiológico importante del ezcema infantil quedarían sin explicación muchos fenómenos clínicos concernientes o relacionados con la enfermedad y por lo tanto que es posible que otros elementos ademas del citado jueguen un papel también importante y que el considerarlos permita al médico entender mejor las numerosas y complejas características de su curso, pronóstico y terapéutica, el autor hace la presente contribución al estudio de los factores no alérgicos del eczema en su etiología y evolución, basándose en la hipótesis de que el eczema se desarrolla en ciertos lactantes predispuestos porque sus madres no les prodigan en forma adecuada el contacto físico agradable o apacible, en otras palabras, su cariño manifestado físicamente, caricias, arrullo, abrazos, etc.

Para probar la validez de esta hipótesis el autor hizo una investigación en un grupo de 25 madres, cuyos hijos de menos de 2 años tenían eczema infantil, comparándolos con 18 casis control, la cual reveló que el 60% de las madres de los niños con eczema, no levantaban o no cargaban a sus hijos

cuando estos lloraban a menos que hubiera alguna molestia física evidente, mientras que en el grupo control solo el 16.6% lo hacía con dicho motivo.

Este hallazgo fué considerado como índice de que la mayoría de los niños eczematosos no recibían el contacto acariciador materno adecuado. Aunque el estudio se planeó para probar la posibilidad de una falta cuantitativa de contacto físico materno-infantil, no elimina la posibilidad de que los aspectos cualitativos de dicho contacto sean también de significación.

Se tuvo buen cuidado de eliminar la posibilidad de que el cambio o disminución en el manejo del niño no fuera a continuación mas bien que precediendo el desarrollo del eczema puesto que es plausible que este hiciera repugnante al niño ante los ojos de la madre o que demandara mucho tiempo de ella, pero hubo buenas pruebas sin embargo, de que dicha explicación era incorrecta y en varios casos fué posible demostrar definitivamente que el manejo inadecuado del niño había precedido mas que seguido al desarrollo de la erupción.

Los resultados de esta investigación estan de acuerdo con los hallados incidentalmente por Spitz, en niños de 6 a 12 meses de edad que habían sido separados de sus madres y vivían en una casa de cuna en quienes había una gran incidencia de eczema, que muy probablemente recibían mucho menos atención, incluyendo contacto físico, que cuando vivían al lado de sus madres. El mismo Spitz, posteriormente en un trabajo reciente destinado específicamente a estudiar los niños con eczema observó que sus madres les brindaban muy poco contacto físico, trabajo que fué desconocido por el autor del artículo presente cuando este inicio su estudio, pero ambos llegan a las mismas conclusiones.

Se penso que la falta de caricias y abrazos de la madre para el niño era de gran significación aun quizás etiológica, pronóstica y terapéutica aunque los datos recogidos no eliminaron la posibilidad de otros factores de igual importancia tales como la predisposición constitucional y la alergia.

La reticencia de las madres para brindar un contacto apacible con la piel del niño era el resultado de su deseo de libertarse de la carga que significaban el cuidado y responsabilidad de un niño y generalmente justificaban su conducta diciendo que no querían "consentir" a sus hijos. En un grupo mas pequeño de madres es muy probable que su falta relativa de caricias fuera motivada por su fatiga o debilidad física.

El autor recomienda que el médico debe ayudar a las madres con niños eczematosos haciendo que se sientan mas satisfechas, con mas soltura y mas capaces en su papel materno y cita los benéficos resultados obtenidos por Williams en estos enfermos haciendo cambiar la actividad de las madres hacia sus hijos, convenciéndolas de que deben de darles mas cariño y caricias que previamente, que en otras palabras significa un contacto físico apacible, tanto cualitativa como cualitativamente.

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PRESSURE-TIME RELATIONS IN THE SAFE CORRECTION OF ATELECTASIS IN ANIMAL LUNGS

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THE resuscitation of a newborn infant presents a unique problem because his lungs have never been expanded. Neonatal atelectasis persists until the infant has made an initial respiratory effort in air.[1] Although Wilson and Farber[2] have shown that air pressures greater than 25 cm. H_2O are necessary to expand the lungs of newborn infants, current opinion favors resuscitation devices which deliver positive pressures considerably less than 25 cm. The reason for the recommendation that low pressures be used is that occasionally lungs have been injured, even by pressures below the range required to correct atelectasis.[3]

The force (hereafter called inflating pressure) which inflates lungs is a pressure difference between trachea and pleura. It is immaterial whether this difference is produced by elevating the pressure in the trachea or lowering the pressure in the pleural space.[4]

The newborn infant, including the premature, can exert inflating pressures 2 to 3 times that considered safe for use with resuscitators. This was shown by Smith and Chisholm,[5] using a face-mask manometer device. When the airway was suddenly occluded for a few seconds, the inflating pressures produced by the infant in struggling for a breath were usually above 40 cm. H_2O.

It is the object of this study to present experimental observations, using animal lungs, designed to shed light on how the infant may be able to exert high inflating pressures without injury to his lungs. This knowledge should be useful in pointing the way to further research in the problem of the resuscitation of apneic newborn infants.

THEORY

The hypothesis which was tested in the following observations is that injury to a lung arises from distention, not from pressure, and that distention is proportional not only to pressure but to the time during which the pressure is exerted. According to this hypothesis, any pressure applied for a sufficiently short interval is safe, and any interval of time is safe if pressures are sufficiently low. In order to open an atelectatic lung, however, a certain minimum pressure must be exceeded. To do this safely, the duration of the application of pressure must be controlled accurately.

METHODS

Preparation of Lungs: Most of the observations have been made on lungs of young animals because of their availability and their freedom from disease.

Rat lungs were removed from animals weighing between 100 and 120 gm. To secure normally

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expanded lungs, rats were killed with nembutal® and ether. Atelectatic rat lungs were prepared as follows: the anesthetized rat was allowed to breathe 100% oxygen for 4 to 5 min. and then the trachea was occluded. Absorption of gas from the air sacs resulted in atelectasis and death (Fig. 1).

Uteri containing fetal pigs were obtained from the slaughter house. Usually 2 to 5 hr. had elapsed before pigs were removed from uterus. It was difficult to excise pig lungs without producing small tears in the pleura, so the lungs were inflated in situ.

Fetal rabbit lungs were obtained by dissection from fetuses removed operatively from the mother at term.

Apparatus: A glass cannula was tied into the trachea and the lung suspended thereby in an air

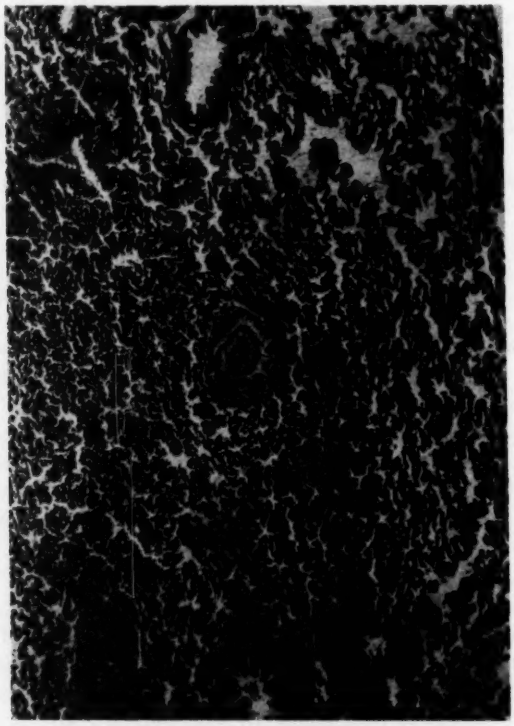


FIG. 1. Microscopic view of adult rat lung, rendered atelectatic as described.

plethysmograph. Figure 2 shows how the apparatus was arranged. Cannula (A) was connected to a Y tube (B), one arm of which was open to room air and the other to a reservoir of air (C) which was filled to any desired pressure by an automatic pump (D). A valve (E) was connected to Y tube so that normally the tracheal cannula was connected to room air. Upon closure of valve (E), cannula was closed to the room and opened to pressure reservoir. A timing device operated by a synchronous motor controlled the valve.

Displacement of air by the expanding lung produced motion of writing lever (F). By use of a small capacity Brodie bellows, the lever operated smoothly at a pressure of about 1 cm. H_2O. The kymographic record represents volume change of lung and not pressure change within the lung. Pressures applied during the observations were measured in U tube connected to the pressure reservoir but they were not continuously recorded. At the combinations of pressure and time used, the stated pressures are the same as those which reached the cannula. Measurements have not been made, however, of pressure gradients within the tracheo-bronchio-alveolar system.

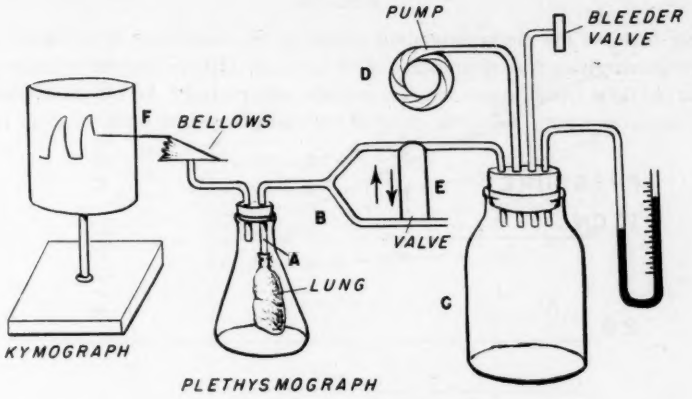
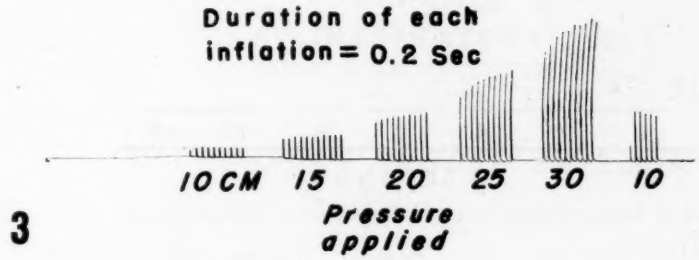


FIG. 2. Diagram of apparatus.



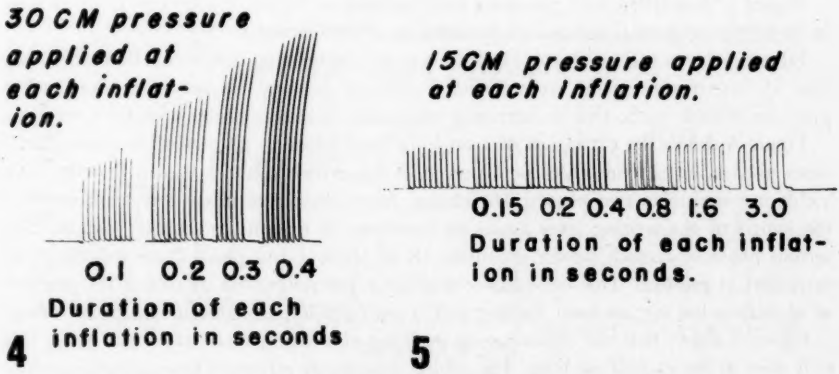

30 CM pressure applied at each inflation.
0.1 0.2 0.3 0.4
Duration of each inflation in seconds
4
15CM pressure applied at each inflation.
0.15 0.2 0.4 0.8 1.6 3.0
Duration of each inflation in seconds.
5

FIG. 3. Kymographic record of expansions of normal rat lung subjected to progressively increasing pressures.

FIG. 4. Kymographic record of expansions of normal rat lung subjected to inflations at constant pressure for successively longer intervals.

FIG. 5. Similar to Fig. 4 except that pressure used was half as great.

Results

Figure 3 shows the plethysmographic record of the expansions of a normal rat lung when progressively increasing pressures of 10 to 30 cm. H_2O are exerted in pulses of fixed duration. In these circumstances expansion varies with pressure. An incidental observation is that the excised lung shows the effect of the preceding expansions, since 10 cm. H_2O

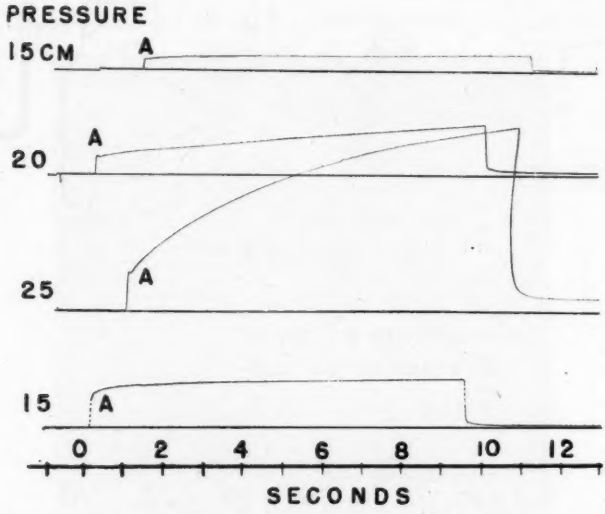


Fig. 6. Ten-second exposures to 3 different pressures. Normal rat lung.

causes a greater change in volume at the end of the record than at the beginning.

Figure 4 shows that with pressures held constant at 30 cm. H_2O, there is an increase in distention with each increase in the duration of the pressures.

Figure 5 shows that at 15 cm. H_2O, time makes little or no difference. It is interesting that 15 cm. is a frequently recommended inflating pressure for use on babies. Such a pressure, though ineffective in correcting atelectasis, is certainly safe, even for a rat lung.

Figure 6 shows the expansion of a rat lung in response to a series of increasing pressures exerted in each instance for 10 seconds. From this record it is seen that the lung yields to pressure in two phases. The change from phase 1 to phase 2 is so abrupt that the inertia of the writing lever causes an overshoot of the line as seen at point A. The second phase is a much slower expansion. Both phase 1 and phase 2 are influenced by variations in pressure. This two-phase expansion is interesting but its rôle in the problem of atelectasis has not yet been clarified and is not considered further in this presentation.

Figure 7 shows that the expansion of the lung of a living man varies with time, just as it does in the excised rat lung. The subject voluntarily refrained from breathing while in a Drinker respirator which was operated to give the pressures indicated in the figure. These inflating pressures were negative over the body, which is essentially the same as positive pressures exerted at the larynx.[4]

Figure 8 shows the results obtained on a pair of rubber balloons which were placed in two plethysmographs and arranged to actuate levers writing simultaneously, one above the

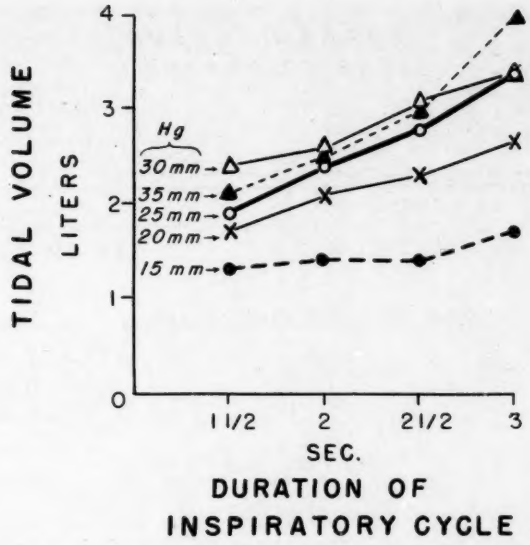


FIG. 7. Influence of time upon tidal air of man in Drinker respirator.

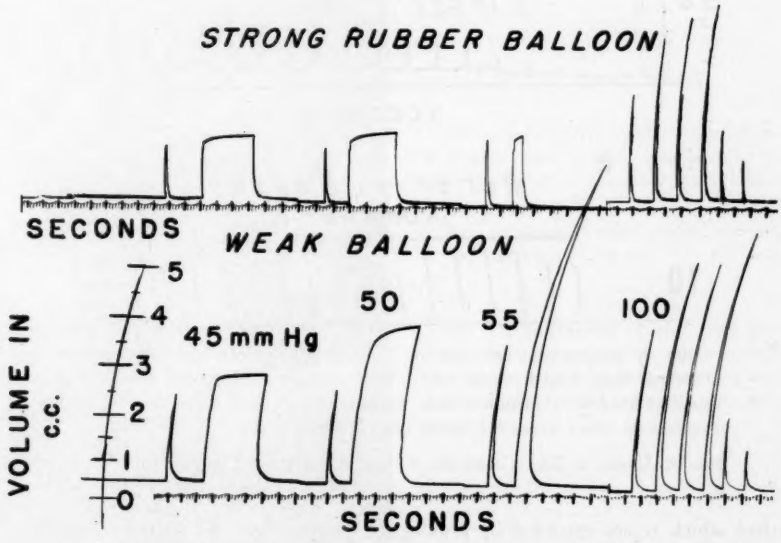
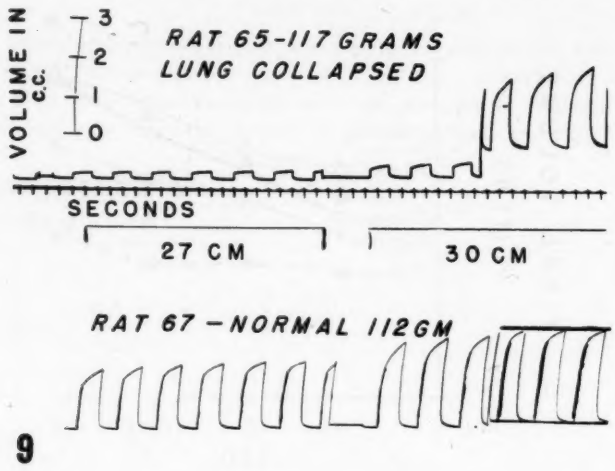


FIG. 8. Kymographic record of expansions of 2 balloons inflated simultaneously.

other. One balloon was made of stronger rubber than the other. Increasing pressures in couplets were exerted, each couplet consisting of a brief and a long exposure. At 45 mm.Hg and at 50 mm.Hg, the weak balloon expands more than the strong one, but the longer exposure in each couplet shows that at these low pressures, a maximum is



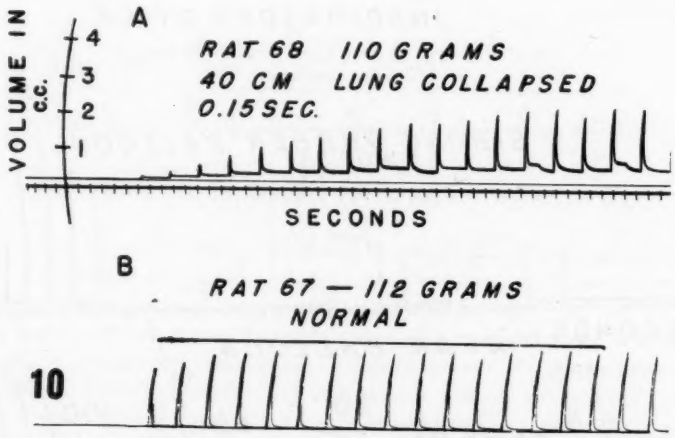
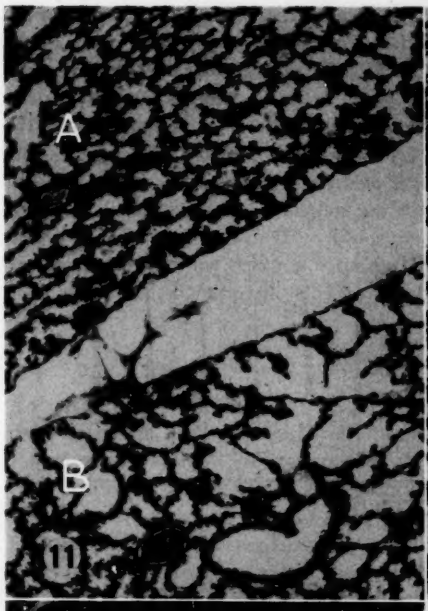


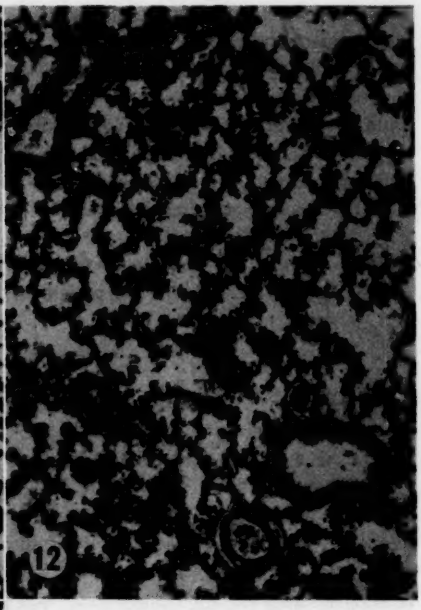
FIG. 9. Simultaneous inflations of 2 rat lungs, upper record being that of atelectatic lung. Fourth movement of lever after 30 cm. pressure was used is actually record of 10 inflations made with kymograph drum motionless, in order to compress entire record into easily photographed length.

FIG. 10. Similar to Fig. 9, with 40 cm. H_2O pressure being applied for 0.15 sec.

reached which is not exceeded by prolonging the exposure. At 55 mm., however, the weaker balloon continues to expand and would have broken had the exposure not been terminated. At 100 mm. applied for varying but brief periods, both balloons can be made to expand, without the weaker one being expanded excessively.

Figures 9 and 10 are records of two lungs inflated simultaneously just as in the case of the balloons. The upper record is that of a rat lung rendered atelectatic as described and the lower that of a normal rat lung. The normal lung is intended to imitate as





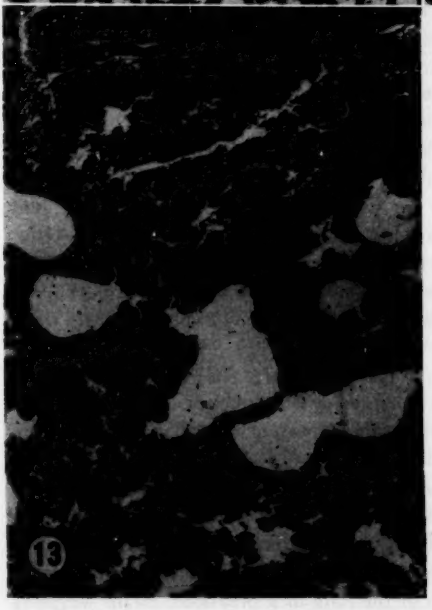


FIG. 11. A. Fetal rabbit lung at term. B. Another lobe of same lung after series of inflations at 35 cm. H_2O for 0.1 sec.

FIG. 12. Lung of term piglet subjected to 135 inflations at 45 cm. H_2O for 0.15 sec.

FIG. 13. Emphysema of atria with persistent atelectasis in lung of 880 gm. infant who died at 4 hr. of age. Excised lung was subjected to 58 inflations at 40 cm. H_2O for 0.15 sec.

nearly as possible the normal portions of a partially expanded single lung and the collapsed lung plays the rôle of the unexpanded parts of a single lung. The object was to find what combination of pressure and time is effective in correcting the atelectasis with the least expansion of the control lung. In figure 9 the duration of the pressures

was long, about 1.5 seconds, and this record is intended to demonstrate the effect of the current methods of infant resuscitation. As a matter of fact, however, no expansion of the collapsed lung was obtained even at 27 cm. H_2O, which is well above the highest pressure obtainable on one popular resuscitator.[6] At 30 cm. H_2O, the collapsed lung did expand and the amount of distention of the control lung may be noted from the line drawn at the top of the spikes. In figure 10 one sees the results with the same control lung, but with another collapsed lung substituted in the upper plethysmograph. At 40 cm. H_2O applied for 0.15 seconds, it is seen that correction of the atelectasis occurred, and that the ex-

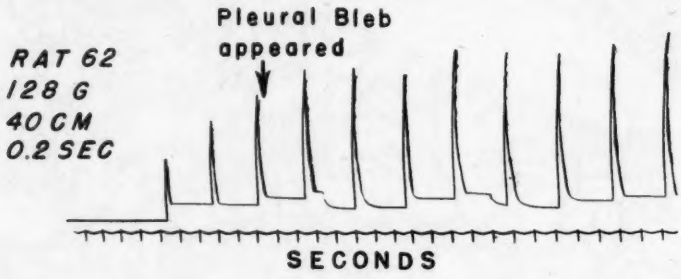


FIG 14.

pansion of lung 67, the control lung, was at no time as great as it had been in the immediately preceding experiment. Seventeen pairs of rat lungs behaved similarly. The conclusion is that since high and effective pressures can be used without overdistention of the control lung, such pressures might also be both safe and effective in opening the lungs of fetal animals which have not breathed in air.

Figure 11 is a photomicrograph of sections taken through two lobes of a lung of a fetal rabbit which died *in utero*. The bronchus to one lobe (section at A) was occluded by a ligature and thus became the control for the experiment. The remainder of the lung was subjected to a series of inflations at a pressure of 35 cm. H_2O for 0.1 second (section at B). Good inflation of the latter portions of the lung resulted. Microscopically, there is no evidence of overexpansion. Grossly, the obstructed lobe appeared totally collapsed, and the microscopic section (Fig. 11 A) was characteristic for newborn animals which have not breathed in air.

Figure 12 is a photomicrograph of a section of the lung of a fetal pig whose lung was satisfactorily expanded at 45 cm. H_2O at a duration of 0.15 seconds for a total of 135 applications. Microscopically, the lung parenchyma appeared well inflated without any evidence of overdistention of the alveolar sacs or alveoli.

No combination of pressure and time has been found which will open lungs of immature animals or infants so that the microscopic sections show normally expanded alveoli. Grossly, such lungs seem to expand fairly well, but microscopically there is marked overdistention of the bronchi and alveolar sacs without any inflation of the alveoli. Figure 13 is a photomicrograph of a section of the lung of a premature infant weighing 880 gm. who died at four hours of age. Pressures of 40 cm. H_2O were applied at a duration of 0.15 seconds for 58 times. This same appearance was noted in the lungs of very immature animals.

Figure 14 is the plethysmographic record of the inflations produced in an atelectatic

adult rat lung. A pressure of 40 cm. H_2O at a duration of 0.2 seconds produced a subpleural bleb which appeared after the third exposure. This injury demonstrates the dangers involved. A difference as small as that between 0.15 and 0.2 seconds may separate a safe from an unsafe interval.

Measurements of the duration of the initial inspiratory gasp of newborn infants have not been made by the present authors or others, so far as is known. Clinical observation suggests that the first gasp is brief. Miller[7] has found that newborn infants during quiet breathing have an average duration of the inspiratory phase of respiration which is usually somewhat less than 0.5 seconds and ranges from 0.25 to 0.7 seconds. An important task for future research is the precise description of the infant's own initial inspiratory efforts, so that positive pressure resuscitation can be made to imitate nature more closely.

Discussion

Atelectasis in adult and fetal animal lungs can be safely corrected at pressures of the order of 40 cm. H_2O applied for a time interval of 0.15 seconds or less. Atelectasis in animal lungs requires a greater pressure for correction than is needed to produce adequate expansion of the nonatelectatic lung, confirming the observations of Wilson and Farber.[2] The time interval which is used for any particular pressure is critical; even a change from 0.15 seconds to 0.2 seconds may represent the difference between a safe and a dangerous interval. Experiments on paired lungs show that the safety of short exposures lies in the small amount of distention of the control lung. It seems likely that rupture is a result of overdistention, whether this distention is produced by too high a pressure or too long an application of a lower pressure.

The work of others suggests that the pressures exerted by normal infants are similar to the pressures which have produced the best results in the experiments on animal lungs. Although exact measurements of the initial inspiratory gasps of infants have not been made, observation suggests that they are brief.

Summary

Observations on animal lungs have been made which support the following statements:

Injury to lungs is caused by overdistention.

Distention is related to time as well as to the pressure exerted.

A certain minimum pressure must be exerted to correct atelectasis. To employ this pressure safely, its duration must be limited.

The combinations of pressure and time which produce satisfactory inflation in rat, rabbit and pig lungs are very similar to each other. Research is needed to find the combinations which are utilized by the normal newborn infant and which might be suitable in positive pressure resuscitation.

No practical application has so far been attempted of the methods of inflation which have been described. Small differences in the duration of each positive pressure inflation determine the safety of the procedure. Clinical application is a subject for future research.

References

1. Smith, C. A., Physiology of Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1946, p. 58.
2. Wilson, J. L., and Farber, S., Pathogenesis of atelectasis of new-born, Am. J. Dis. Child. **46**:590, 1933.

3. Wilson, R. A., Torrey, M. A., and Johnson, K. S., Initiation of respiration in asphyxia neonatorum: Clinical and experimental study incorporating fetal blood analyses, Surg., Gynec. & Obst. **65**:601, 1937.
4. Maloney, J. V., Jr., and Whittenberger, J. L., Clinical implications of pressures used in body respirator, Am. J. M. Sc. **221**:425, 1951.
5. Smith, C. A., and Chisholm, T. C., Intrapulmonary pressures in newborn infant, J. Pediat. **20**:338, 1942.
6. Kreiselman, J., Improved apparatus for treating asphyxia of newborn infant, Am. J. Obst. & Gynec. **39**:888, 1940.
7. Miller, H. C., Personal communication to the authors.

SPANISH ABSTRACT

Relación entre el Grado de Presión y su Duración en la Corrección sin Riesgo de la Atelectasia en Pulmones de Animales

El objeto de este estudio es presentar las observaciones experimentales hechas en pulmones de animales sometidos a presiones de intensidad y duración variables para lograr su distensión alveolar y que lesiones indescables pueden producirse, que rindan información útil en la resucitación del recién nacido.

Aunque se ha mostrado que presiones mayores de 25 cm. de agua son necesarias para expander los pulmones del recién nacido, la opinión que prevalece favorece a los resucitadores mecánicos que dan presiones positivas considerablemente menores que 25 cm. pues ocasionalmente se han lesionado pulmones aun con presiones abajo de los límites requeridos para corregir la atelectasia, pero, por otro lado es curioso que el recién nacido, aun prematuro, puede ejercer presiones 2 a 3 veces mayores que las consideradas como seguras en el uso de los respiradores.

Al planear sus observaciones los autores trataron de verificar la hipótesis de que la lesión del pulmón es producida por la distensión no por la presión y que la primera es proporcional no solo a la presión sino también al tiempo durante el cual dicha presión actúa. De acuerdo con esta hipótesis cualquier presión es segura cuando se aplica por un lapso de tiempo suficientemente corto, así como cualquier lapso es seguro si las presiones son lo suficientemente bajas. Sin embargo, para abrir un pulmón atelectásico se debe exceder cierto mínimo de presión y para hacerlo sin riesgo, la duración de la aplicación de la presión debe controlarse con exactitud.

Las observaciones que realizaron los autores les permiten hacer las siguientes afirmaciones: la lesión pulmonar es producida por distensión excesiva y esta en relación tanto a la duración de la presión como a su magnitud. Se necesita ejercer un mínimo de presión para corregir la atelectasia pero para que ésta no represente un peligro se debe limitar su duración. Las combinaciones de la intensidad y duración de la presión que producen la expansión de los pulmones de la rata, conejo y cerdo son muy similares. Se necesita investigar la combinación que utiliza el recién nacido normal que sea adecuada en la resucitación por presión positiva.

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BAL THERAPY IN CHRONIC LEAD POISONING

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THERE has been considerable controversy regarding the treatment of chronic lead poisoning with specific therapy. Aub[1, 2] and his associates, investigating the lead content of bone and urinary excretion of lead in animals and patients with plumbism, demonstrated that lead in the body is absorbed, transported, deposited and excreted much in the same manner as is calcium. They showed that conditions which favor calcium retention simultaneously favor deposition of lead in the bones and, conversely, factors which tend to produce mobilization of calcium from the bones also tend to liberate lead from its skeletal deposits. It is universally accepted that infections or metabolic disorders which cause acidosis will liberate lead and calcium from the depot sites. Because accidental or incidental mobilization of lead will cause an acute exacerbation of symptoms in chronic plumbism, the question arises as to whether lead stored in the tissues should be permitted to remain or whether attempts to mobilize it should be made. Since attempts at mobilization may also result in a recurrence of symptoms, opposing views have been taken on the problem. However, if a substance could be found which would mobilize lead from the tissues and transport it in the form of a nontoxic, nonionizable complex to the kidneys for excretion, it would be better to promote the excretion of lead under supervision when the patient is in apparent good health. Several such agents are believed to accomplish this result.[3-7] One of these substances, known as BAL (2, 3 dimercaptopropanol [dimercaprol®]) has been used by many investigators with supportive measures in the treatment of acute lead encephalopathy.[8-11] Ennis[8] used BAL on 16 patients with acute lead encephalitis. His conclusion was that BAL lowered the mortality and probably the severity of residua of severe lead encephalopathy. However, many investigators still remain skeptical of the value of BAL in plumbism because they feel that the lead-BAL complex is not as stable as other metal complexes, and that lead may return to a soluble form in the blood stream.

It is the purpose of this paper to attempt to demonstrate that BAL will mobilize lead from its depot sites, that the lead-BAL complex is stable and that BAL itself is a safe therapeutic agent.

MATERIALS AND METHODS

Patients included in this study were part of a group of 14 cases of plumbism already reported by the authors.[12] Diagnosis of lead poisoning was based on a history of pica, characteristic signs and symptoms of the disease, basophilic stippling of red blood cells, increased density at ends of long bones and demonstration of excessive amounts of lead in urine. Hematologic and blood chemical studies, spinal fluid analyses and urinary estimations of lead were made before, during and after BAL therapy and may be found in tables 1, 2, 3 and 4. Reproductions of roentgen films of Case 1 are included in the report as representative of the entire group of roentgenograms. The estimations of urinary lead were made by the dithizone method of Kaye.[13]

From Kings County Hospital, Brooklyn.
(Received for publication June 12, 1952.)

TABLE 1

HEMATOLOGY

	Date (1951–1952)	Hgb. (gm./100 cc.)	WBC (thousand)	Neutrophiles	Lymphocytes	Monocytes	Eosinophiles	Basophiles	Basophilic tippled RBC/16 RBC
Case 1	12/5	7.5	10	40	48	0	12	0	400
	12/29*	9	16	64	28	4	4	0	0
	1/15	9	10	58	32	2	7	1	0
Case 2	2/15	10	9.8	66	26	7	0	0	0
	3/4*	10	16	67	22	7	2	0	0
	3/17	10	10	44	52	4	0	0	0
Case 3	4/17	9	8	46	49	5	0	0	0
	5/5*	9	7.5	44	51	5	0	0	0
	5/13	9	8.6	50	46	4	0	0	0

* On therapy.

TABLE 2

BLOOD CHEMISTRY

	Date (1951–1952)	Urea (mg./100 cc.)	Sugar (mg./100 cc.)	Calcium (mg./100 cc.)	Phos. (mg./100 cc.)	Alk. Phosphatase (Bodansky U.)	Total Protein (gm./100 cc.)	A/G	Cephalin Flocculation
Case 1	12/29*	34	110	10.0	4.4	—	8.0	5.6/2.4	Neg.
	1/7	30	107	10.8	4.6	—	8.3	5.8/2.5	Neg.
Case 2	2/13	23	107	9.8	4.4	3.2	7.4	5.7/1.7	Neg.
	2/25*	28	110	9.8	4.2	1.5	8.0	6.3/1.7	Neg.
	3/5*	29	112	10.8	5.3	3.1	8.5	5.9/2.6	—
	3/14	26	97	10.1	4.4	5.0	8.6	5.5/3.1	Neg.
Case 3	4/21	28	123	9.8	4.6	6.9	7.0	6.2/0.8	Neg.
	5/5*	21	132	10.3	4.4	5.6	8.0	5.6/2.4	Neg.
	5/13	25	110	10.2	4.0	6.3	6.9	4.9/2.0	Neg.

* On therapy.

CASE REPORTS

Case 1 (L. C.): A Negro male 3 yr. of age was admitted to Kings County Hospital because of pain in knees, vomiting and constipation of 3 wk. duration. Patient had been licking recently repainted walls in his home for several months. A diagnosis of lead poisoning at that time was substantiated by basophilic stippling of red blood cells, roentgenographic evidence of increased density at ends of long bones and finding of lead 0.1 mg./l. of urine.

Patient was treated with a high calcium, inorganic phosphate and vitamin D intake. Hospital course was uneventful and he was discharged in 2 wk.

During course of the next 4 mo. he was followed in outpatient department. Patient suffered from recurring episodes of pain in knees, vomiting and constipation. He was readmitted to the hospital then to be treated with BAL.

TABLE 3

SPINAL FLUID FINDINGS

	Date (1951–1952)	Color	Pandy	Cells	Total Protein (mg./100 cc.)	Chlorides (mg./100 cc.)	Sugar (mg./100 cc.)
Case 1	12/7	clear	0	4 Lymph	23	753	71
	12/19*	clear	0	0	14	750	60
	1/7	clear	0	0	21	696	58
Case 2	2/11	clear	0	0	21	707	58
	2/28*	clear	0	0	20	700	60
	3/14	clear	0	0	18	698	66
Case 3	4/17	clear	0	0	9	692	80
	5/5*	clear	0	0	16	733	76
	5/13	clear	0	0	23	790	42

* On therapy.

TABLE 4

URINARY LEAD CONTENT

Case 1			Case 2			Case 3		
Date 1951–52	Lead Content		Date 1952	Lead Content		Date 1952	Lead Content	
	mg./l.	mg./24 hr.		mg./l.	mg./24 hr.		mg./l.	mg./24 hr.
12/10–12/12*	0.250	0.114	2/13–2/15*	0.293	0.085	4/19–4/21*	0.206	0.090
12/12–12/14*	0.448	0.132	2/15–2/17*	0.225	0.051	4/23–4/25	0.384	0.178
12/14–12/16	0.338	0.168	2/17–2/19	1.440	0.328	5/1 –5/3	0.496	0.280
12/16–12/18	0.413	0.368	2/19–2/21	2.240	0.549	5/9 –5/11	0.470	0.159
12/18–12/20	0.402	0.245	2/21–2/23	0.606	0.303	5/16–5/18*	0.157	0.077
12/20–12/22	1.050	0.590	2/23–2/25	0.697	0.480			
12/22–12/24	0.765	0.372	2/25–2/27	0.547	0.545			
12/24–12/26	1.190	0.574	2/27–2.29	1.100	0.545			
12/28–12/30	1.200	0.549	2/29–3/2	0.653	0.392			
12/30–1/1	1.170	0.476	3/2 –3/4	0.972	0.512			
1/1 –1/3	1.071	0.476	3/4 –3/6	1.140	0.570			
1/3 –1/5*	0.600	0.408	3/6 –3/8	0.631	0.399			
1/5 –1/7*	0.500	0.248	3/8 –3/10*	0.235	0.123			
1/14–1/16*	0.225	0.098	3/10–3/12*	0.263	0.171			
			3/12–3/14*	0.244	0.128			

* Without treatment.

BAL therapy was begun 10 days later. He was given 4 mg./kg. body weight of a 10% solution of the substance in benzyl benzoate and oil intramuscularly every 4 hr. around the clock for 20 days continuously. Elixir benadryl®, 1 teaspoon 3 times daily, was given to forestall nausea and vomiting. Urine was collected through an indwelling catheter into a specially prepared container and sent for determination of lead every 48 hr. Crysticillin 1 cc. was given daily to suppress urinary infection. Urinary lead output before BAL, in response to BAL, and after BAL is shown in table 4

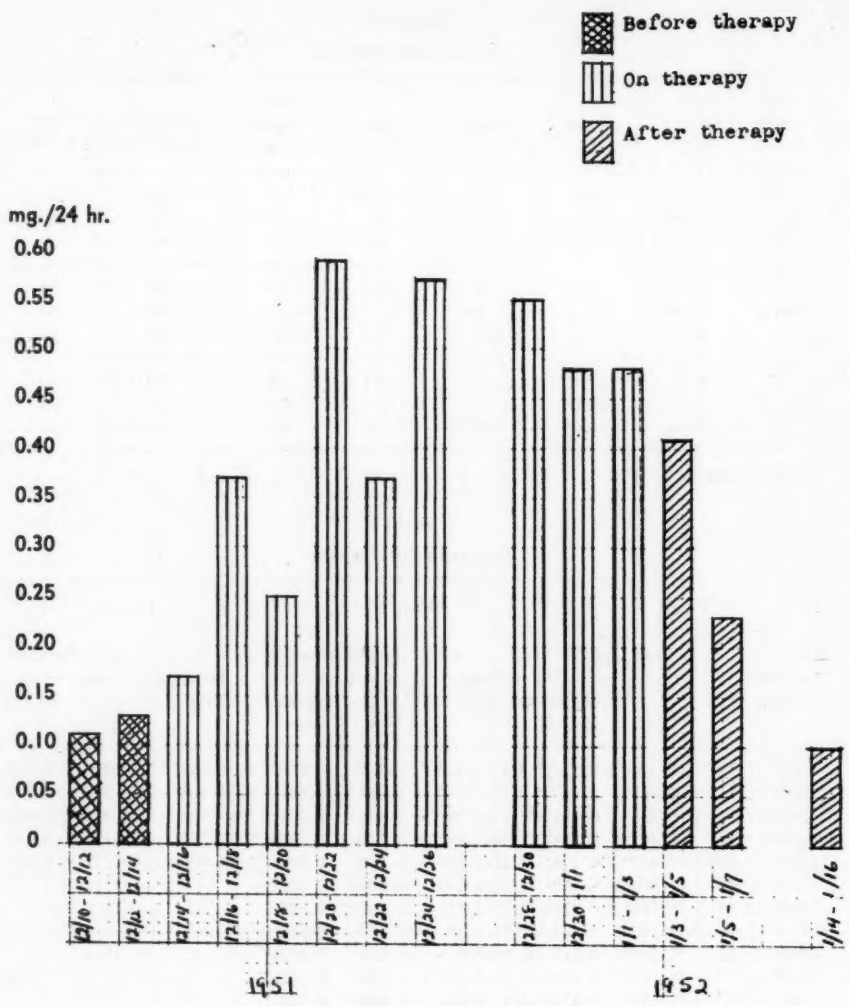

CHART 1. Case 1, urinary output of lead.

and chart 1. Resting lead output was raised 5 to 7-fold on BAL and then dropped to previous level after discontinuance of BAL. Patient was free of knee pain on 3rd day of therapy and bowel movements returned to normal by 7th day. At no time was there an exacerbation of symptoms of plumbism despite high levels of lead obtained in urine. There were no toxic symptoms due to BAL and no adverse effects of this drug were noted on the hematopoietic system, urinary system or liver function tests (tables 1 and 2). Routine urinalyses showed no abnormalities. No changes occurred in spinal fluid (table 3). Roentgenograms of ends of long bones before and after treatment showed a significant decrease in densities (Figs. 1 and 2).

Case 2 (P. I.): A white female 3 yr. of age was admitted to Kings County Hospital for a L-sided tonic convulsion followed by a coma. Patient had been irritable and vomiting for 1 wk. prior to convulsive episode. It was learned that she had been chewing on window sill paint for past 6 mo. A

diagnosis of lead poisoning was substantiated by finding basophilic stippling of red blood cells, roentgenographic evidence of increased density at ends of long bones and report of lead 0.375 mg./l. of urine. Lumbar puncture revealed spinal fluid under pressure of 250 mm. H_2O. Estimation of total proteins was 89 mg./100 cc. fluid and cell count was 9 lymphocytes. Fundoscopic examination showed bilateral choked optic discs.

Patient was treated with a high calcium, inorganic phosphate, and vitamin D intake. She remained in coma for 2 days after initiation of therapy. When she recovered from coma it was noted that she had a L facial palsy and a L spastic hemiparesis. She was discharged after 18 days with the above neurologic residua. She was, however, able to walk unsupported.

One month after discharge patient began falling to the ground. She was readmitted to hospital 7 mo. after discharge because of increasing frequency of these falling episodes.

It was found that patient fell 15 times an hour. While standing or walking, she would suddenly drop. The fall was caused by unexpected buckling of knees and was accompanied by flexion at the

FIG. 1. Case 1: Increased density at distal ends of fibula and tibia. Before BAL therapy.

FIG. 2. Case 1: Decrease in density at distal ends of fibula and tibia. After BAL therapy.

hips. There was no loss of consciousness and patient would rise almost immediately unaided. Even while sitting she would suddenly pitch forward at the waist and then recover her position in a matter of seconds. She still had a L spastic hemiparesis. In addition, there was atrophy of the L deltoid muscle.

Six days later, patient was placed on exactly the same therapeutic regime as patient in Case 1. Urinary lead was determined every 48 hr. Again the urinary lead level on BAL rose to 5 to 7 times the resting output (table 4, chart 2). RGs of long bones after treatment showed a definite decrease in densities. There was no exacerbation of symptoms of plumbism, no toxic symptoms due to BAL, and no disturbance in blood, kidney or liver (tables 1 and 2). Routine urinalyses showed no abnormalities.

The patient was observed in hospital for an additional 2 wk. after BAL therapy. The number of falls began gradually to decrease in number. Patient was discharged asymptomatic 6 wk. later. Two months after discharge she is still able to walk and play without falling.

Case 3 (A. H.): A Negro female 2½ yr. of age was admitted to Kings County Hospital for a generalized tonic convulsion followed by a severe ataxia. It was learned that she had been chewing on wall paint for 4 mo. A diagnosis of lead poisoning was established by roentgenographic evidence of increased density of ends of long bones and finding of lead 0.16 mg./l. urine. There was no basophilic stippling of red blood cells. Hgb. was 5 gm./100 cc. blood. Lumbar puncture revealed spinal fluid under pressure of 300 mm. H_2O, 10 lymphocytes and total proteins 12 mg./100 cc. fluid. Fundoscopic examination showed bilateral choked optic discs.

Patient was treated with high calcium, inorganic phosphate, and vitamin D intake. She was discharged home asymptomatic after 10 days.

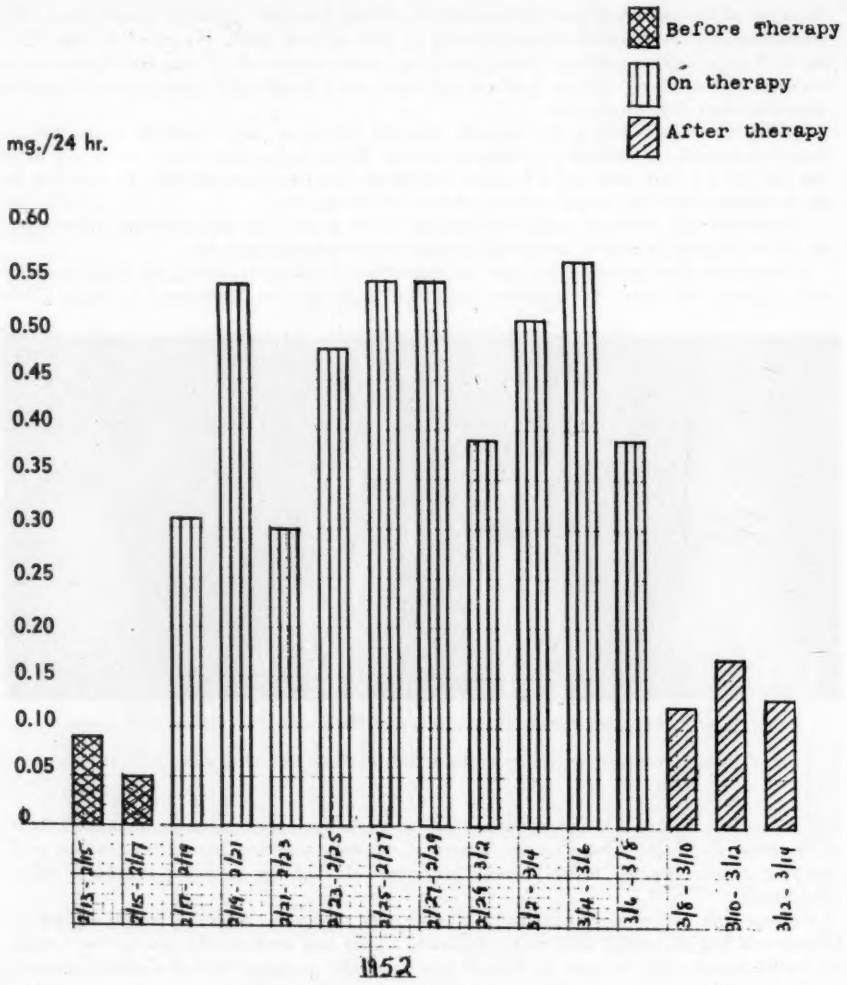

CHART 2. Case 2, urinary output of lead.

Patient was seen every 2 mo. in the outpatient department. She remained asymptomatic for a year and then began falling to the ground. She was readmitted to the hospital after 6 wk. As in Case 2, falls were caused by buckling at knees and were accompanied by flexion at hips. There was no loss of consciousness. Patient arose immediately unaided. These episodes occurred about 10 times a day. She had hyperactive deep tendon reflexes, bilateral Babinski sign and ankle clonus.

BAL therapy was started after 1 wk. She received BAL in the same doses as in preceding cases. After resting urinary output of lead was determined, 48 hr. urine specimens were collected on days 3 and 4, 11 and 12, 19 and 20 of BAL therapy. On days 5 and 6 after BAL therapy another 48 hr. specimen was obtained. Table 4 and chart 3 indicate resting urinary output of lead was increased threefold by BAL. RGs of ends of long bones showed marked decrease in densities. No significant

changes were observed in blood chemistry, spinal fluid, liver function tests or urine on BAL therapy (tables 1, 2 and 3). At no time was there an exacerbation of symptoms of plumbism or toxic reaction due to BAL.

Clinical improvement in ambulation was noted by 11th day of therapy. Falling episodes began to decrease in frequency. For 2 wk. following BAL therapy no falls were observed. Patient was discharged asymptomatic in 6 wk.

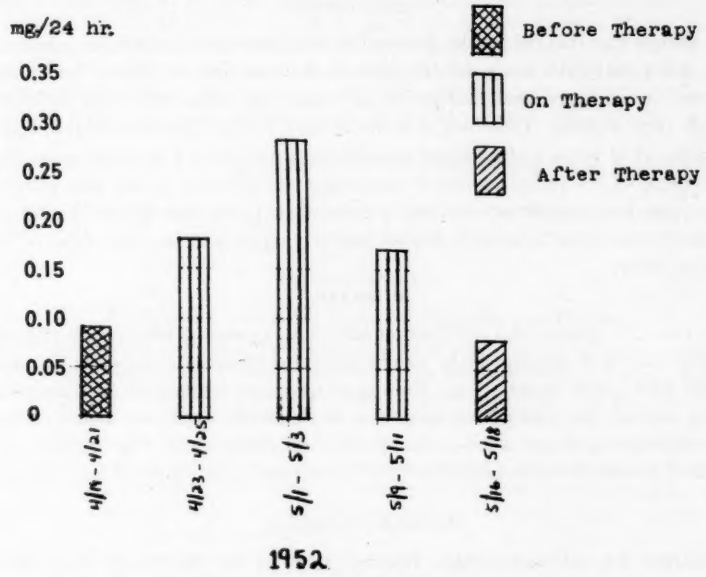

CHART 3. Case 3, urinary output of lead.

DISCUSSION

2, 3, Dimercaptopropanol (BAL) was introduced by Peters[14, 15] and his colleagues as an antidote for the effect of arsenic gases. They demonstrated the effect of arsenic in combining with -SH groups in tissue proteins and the effect of BAL in competing with the tissues for arsenic. BAL reacts with arsenoxides to form nontoxic compounds which are rapidly excreted. BAL has since been shown to promote excretion of other metals such as mercury,[16] gold,[17, 18] silver and copper.[19, 20]

In the present investigation the effect of BAL is seen as clearly related to a mobilization of lead deposited in the tissues. In the patients studied the resting urinary output of lead was raised three to sevenfold. Definite roentgenographic evidence of a decrease in the densities at the ends of long bones was demonstrated (Figs. 1 and 2). Despite the high levels of lead obtained in urine, there was no exacerbation of symptoms of plumbism. No toxic reactions due to BAL was observed in the dosage used. Repeated blood examinations (table 1) did not indicate a decrease in hemoglobin or a leucopenia. Blood chemistry tests (table 2) showed normal values for total protein, A/G ratio, calcium, phosphorus and alkaline phosphatase. Spinal fluid findings were consistently normal and there was no evidence of renal impairment (tables 2 and 3).

Blackman[21] and others[22, 23] have demonstrated that the basic pathology in lead encephalopathy is punctate hemorrhages, gliosis and focal areas of necrosis throughout the

brain. Such pathology is undeniably irreversible. However, the patients in Cases 2 and 3 show that there may be a reversible part in the lesions of lead encephalitis. Lead is deposited in the brain and it may directly injure or kill nerve cells. Therefore, the authors feel that the early use of BAL therapy in lead intoxication will reduce the severity of the residua.

Conclusions

The authors feel that the results obtained in the three cases studied give adequate basis for the belief that BAL has a definite place in the treatment of chronic lead poisoning. Accidental or incidental mobilization of lead from the tissues may lead to irreversible and often fatal sequelae. Therefore, it is the authors' feeling that BAL therapy will result in the removal of active and potential dangers concurrent with lead intoxication. Furthermore, because of its ability to reverse neurologic symptoms it is felt that early use of BAL in acute lead encephalopathy may prevent their appearance altogether. Its demonstrated ability to reverse neurologic residua makes it superior to any other form of therapy thus far available.

Summary

Three cases of chronic lead intoxication have been presented which were treated with BAL in a dose of 4 mg./kg. body weight every four hours for 20 days. Cessation of symptoms were noted in every case. Resting urinary lead levels were increased three to sevenfold without exacerbation of symptoms of plumbism. BAL was found to be nontoxic in the dose used and acted as an effective deleading agent. The authors feel that this form of treatment merits use in both the chronic and acute phases of lead intoxication.

Acknowledgments

The authors are indebted to Mrs. Frances Jacobs of the Toxicology Department of Kings County Hospital for the urinary lead determinations.

References

1. Aub, J. C., Biochemical behavior of lead in body, J.A.M.A. **104**:87, 1935.
2. Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P., Lead poisoning, Medicine **4**:1, 1925.
3. Proctor, C. D., and Kahn, H. D., Disodium hydrogen phosphate therapy in lead poisoning, Am. J. M. Sc. **219**:316, 1950.
4. Bauer, W., and others, Lead poisoning, Medical Grand Rounds, Massachusetts General Hospital, Am. Practitioner **1**:493, 1947.
5. Wilkinson, E. C., Sodium citrate in treatment of lead encephalopathy, Texas State J. Med. **43**:442, 1947.
6. Gedgoud, J. L., Sodium citrate therapy in lead encephalopathy, Nebraska M. J. **31**:48, 1946.
7. Wight, S. C., Lead poisoning in children: Case Report, J. Am. M. Women's Assoc. **2**:448, 1947.
8. Ennis, J. M., and Harrison, H. E., Treatment of lead encephalopathy with BAL, Pediatrics **5**:853, 1950.
9. Ebel, E. H., Chronic plumbism in children, Bull. St. Louis W. Hosp. **3**:16, 1951.
10. Bastrup-Madsen, P., Dimercaprol in acute lead poisoning, Lancet **2**:171, 1950.
11. BAL therapy in lead poisoning: Review of literature, Industrial Hygiene Newsletter, 1949.
12. Giannattasio, R. C., Bedo, A. V., and Pirozzi, M. J., Fourteen cases of lead poisoning, Am. J. Dis. Child., to be published.
13. Gradwohl, R. B. H., Clinical Laboratory Methods and Diagnosis, ed. 4, St. Louis, The C. V. Mosby Company, 1948, vol. 2, p. 2088.
14. Peters, R. A., Stocken, L. S., and Thompson, R. H. S., British anti-lewsite (BAL), Nature **156**:616, 1945.

15. Peters, R. A., British anti-lewisite: Report on its use and therapeutic value in arsenical intoxications from BAL conference, Lancet **2**:497, 1947.
16. Longcope, W. T., and Luetscher, J. A., Jr., Clinical uses of 2, 3 dimercaptopropanol (BAL): Treatment of acute mercury poisoning by BAL, J. Clin. Investigation **25**:451, 1946.
17. Cohen, A., Goldman, J., and Dubbs, A. W., Treatment of acute gold and arsenic poisoning: Use of BAL (2,3-dimercaptopropanol, British anti-lewisite), J.A.M.A. **133**:749, 1947.
18. Ragan, C., and Boots, R. H., Treatment of gold dermatitides, J.A.M.A. **133**:752, 1947.
19. Mandelbrote, B. M., Stanier, W. M., Thompson, R. H. S., and Thurston, M. N., Studies on copper metabolism in demyelinating diseases of central nervous system, Brain **71**:212, 1948.
20. Thompson, R. H. S., and Whittaker, V. P., Antidotal activity of British anti-lewisite against compounds of antimony, gold and mercury, Biochem. J. **41**:342, 1947.
21. Blackman, D. D., Jr., Lesions of lead encephalitis in children, Bull. Johns Hopkins Hosp. **61**:1 1937.
22. McKhann, C. F., Lead poisoning in children: Cerebral manifestations, Arch. Neurol. & Psychiat. **27**:294, 1932.
23. Cantarow, A., and Trumper, M., Lead Poisoning, Baltimore, The Williams & Wilkins Company, 1944, p. 64.

SPANISH ABSTRACT

Terapéutica con BAL en la Intoxicación por Plomo

Aun cuando existen reportes en la literatura referentes al uso del BAL (2-3 dimercaptopropanol) en la intoxicación plómbica con resultados benéficos, existe aún excepticismo a este respecto porque hay investigadores que creen que el complejo BAL-plomo no es estable como con otros metales y que el plomo puede volver a su forma soluble en la corriente sanguínea. Los autores reportan los resultados obtenidos con el tratamiento con BAL de tres casos de intoxicación plómbica crónica administrado a la dosis de 4 mlgs. por kilo de peso cada 4 horas durante 20 días. El diagnóstico se basó en la historia de pica, en los signos y síntomas característicos de la enfermedad, punteado basófilo de los eritrocitos, bandas de densidad aumentada en los huesos largos y la presencia de cantidades excesivas de plomo en la orina.

El estudio de los casos les permitió observar el efecto producido por el BAL claramente relacionado con la movilización del plomo depósitado en los tejidos. Efectivamente, la eliminación del plomo en la orina se elevó de 3 a 7 veces, durante el tratamiento, se apreció simultáneamente una disminución franca de la densidad de las extremidades de los huesos largos, desaparición de los síntomas en todos los casos, no hubo exacerbación de los síntomas de plombismo a pesar de los altos niveles de plomo alcanzados en la orina, ni tampoco reacciones toxicas al BAL. Los examenes de sangre no indicaron disminución en la hemoglobina ni leucopenia, la química sanguínea mostró valores normales de proteínas sanguíneas, del índice albúmina-globulina, calcio, fósforo y fosfatasa alcalina, los exámenes de líquido cefalorraquídeo fueron continuamente normales y no se encontraron signos de insuficiencia renal.

Los autores concluyen por los resultados obtenidos en estos tres casos que el BAL tiene su lugar definitivo en el tratamiento de la intoxicación plómbica crónica, que hace desaparecer sus peligros activo y potencial que ella representa ya que la movilización accidental o incidental del plomo de los tejidos puede conducir a secuelas irreversibles a menudo fatales, mas aún, debido a su posibilidad de reversión de los síntomas neurológicos se cree que su empleo precoz en la encefalopatía plómbica aguda pueda prevenir por completo su aparición.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

Two communications are presented in this issue. The first is by Dr. Edwin A. Harper of Lynchburg, Va., and the second by Dr. Harold D. Lynch of Evansville, Ind.; both currently serving as chairman of the American Academy of Pediatrics in their respective states.

LYNCHBURG, A CITY OF SPECIALISTS

By EDWIN A. HARPER, M.D.
Lynchburg, Va.

THIS description of medical practice in Lynchburg, Virginia, is offered because it presents an unusual pattern for a small city wherein most of the citizens' medical needs are met by specialists rather than by general practitioners. Furthermore, it is remarkable that this pattern has developed spontaneously without any master plan and without any central clinic or hospital or other type of group practice. The great majority of physicians practice independently but in an atmosphere of cooperation. There are now 78 physicians in active practice in the city and some 20 in the adjacent trading area.

Since 1930, 59 new doctors have come to the city and remained. Of these men, 50 limit their practice to a specialty, while 9 are in general practice.

At the present time one might safely estimate that over 75% of the total volume of medical work in the city is performed by specialists and less than 25% by men in general practice. A check of admissions to the Lynchburg General Hospital shows that in 1951

only 13% were patients of general practitioners, even though all physicians in town are on one of the staffs of this hospital. In 1951 general men delivered 471 out of 2,453 live births in the city or 23.8%. Only four mothers were attended by midwives.

Two reasons that are responsible for this situation are the fact that basic minimum fees are the same for specialists and general men and that the public has educated itself to prefer the services of a specialist whenever available. In general, people pick their own doctors in each field and go directly, without being referred, to their internist, pediatrician, obstetrician, otolaryngologist, ophthalmologist, and orthopedist. The internists and pediatricians fill the place, insofar as it can be filled, of the old-time family doctor. All men in these two branches make house visits. In a fair number of instances patients go directly to their own surgeon. They are usually referred to the genito-urinary specialist, the pathologist (clinical laboratory) and the roentgenologist. In this maze of special fields it may seem remarkable that anyone ever finds the right doctor, but in practice there is very little lost motion. The city is small enough for each physician and his special field to be generally known. A person who finds himself in the wrong office is sent on to someone more suitable to hear his complaint and no charge is made for such referral.

Lynchburg is a city of almost 50,000, the center of a trading area of 125,000, near the center of Virginia in the Piedmont section. It is 115 miles west of Richmond and 55 miles east of Roanoke. It is an old city, first settled in 1757, incorporated in 1786, and it has grown slowly but steadily from one census to another. The population was 7,000 in 1860, 19,000 in 1900, 44,000 in 1940. Approximately 25% of the total are Negroes. The city began as a tobacco market and later became a center of tobacco manufacture. It is now supported by a variety of industries with 18,000 workers sharing a payroll of $20,000,000. The shoe industry employs 3,000, textiles 1,800, two foundries 1,300, paper 800, needle trades 800, and some 80 other industries employ the rest. Total bank deposits are 70 millions. The assessed valuation is $75,000,000. Per capita income is estimated at $1,200. This compares with $1,200 for Virginia as a whole and $1,436 for the U.S.A.

Hospitals

There are three hospitals, all with open staffs. Practically all white physicians have privileges in all three. Five Negro physicians have limited privileges at the Lynchburg General Hospital.

The largest hospital is the Lynchburg General Hospital with 158 beds. Two departments are segregated—obstetrics with 31 beds on the third floor and pediatrics, medical and surgical, with 24 beds and cribs in one wing of the fourth floor. Patients in other specialties are not placed in particular areas, but white and colored are separated. The Virginia Baptist Hospital has 100 beds, including a 22 bed obstetric wing. This hospital receives some of its support from Baptists throughout the state. The third hospital is Marshall Lodge Memorial with 80 beds devoted to general medicine and surgery. No obstetrics is done in this hospital and there is no special pediatric department, but there is a detached 35 bed building for the low-cost care of chronic and convalescent patients.

The Baptist and Memorial Hospitals admit only white patients. The Lynchburg General devotes 71 of its 158 beds to the care of Negro patients.

The hospital staffs are quite well departmentalized. For at least 20 years new staff members have been limited to practice in their own specialty. There are, however, a few older men who do general practice and who also have privileges in major surgery and

operative obstetrics under the usual "grandfather clause." Current arrivals in general practice are limited to normal obstetrics and minor surgery.

Clinics

The city of Lynchburg maintains an extensive program of free clinics for the indigent. These are staffed chiefly by specialists who are paid from $5.50 to $9.00 for a single clinic session which lasts from one-half to two hours. There are seven pediatric, four medical, two venereal, one E. N. & T., one TBC, one eye, one obstetric and one dermatologic clinic per week. Indigent surgical and orthopedic patients are seen in the emergency room of the Lynchburg General Hospital.

Distribution in Specialties

Below is a tabulation showing the number of specialists in each field and their status in reference to Board Certification. All of the men shown below limit their work strictly to their own specialty. The two categories labelled "Diplomates" and "Eligible for Certification" are self-explanatory. The next category, "Competent specialists, formal training insufficient for certification" obviously involves an element of judgment on the part of the author. These are men who, in the eyes of the local profession, have proven themselves deserving of this title.

No. of Men in Each Field	Diplomates	Eligible	Competent Specialists Formal Training not Sufficient for Certification
Internal Medicine, 12	5	5	2
Surgery, 8	4	2	2
E. N. & T., 6	2	3	
Eye, 2	1	1	
G. U., 4		4	
Orthopedics, 4	2	2	
Obstetrics, 5	3		2
Dermatology, 1			1
Pediatrics, 6	2	3	
Radiology, 3	2		1
Pathology, 3	1	1	1
Anaesthesiology, 3		3	
General Practice, 22			

There are 17 white physicians and five colored who do general practice. Fourteen white are in active practice and three are relatively inactive because of age. Only 8 of the 14 do obstetrics and only four do any major surgery.

Discussion

The present sketch of practice in Lynchburg is intended as purely descriptive, and not at all as an argument in favor of specialism vs. general practice. No claim is advanced that the pattern is unique; there are doubtless other cities of similar size where more practice is carried on by specialists than by general men. In the wealthier residential suburbs of the large cities the bulk of practice is frequently carried on by specialists.

There are, however, many cities of 100,000 to 200,000 in the East and Middle West where there are fewer specialists than in Lynchburg and where the bulk of medical work is done by men in general practice.

The unusual feature of practice here is the marked preference of each economic group for specialist care. The employees of the cotton mill and the independent storekeepers are equally likely to bring their children to a pediatrician for care. Thus the practice of a majority of physicians reaches all economic levels.

It may be of interest to note that the present system seems to be economically self-sustaining. Doctors who come, stay. Inquiries from physicians who are seeking a location indicate that the majority are trained as specialists.

Those of us who have seen the medical needs of a city cared for in this way are naturally interested in what the future trend will be. Several lively arguments have been started as to the probable result if a number of well trained, aggressive general practitioners should settle here and attempt to turn the tide back to the more usual pattern. In all fairness to those medical leaders who for some years have urged a return to more general practice, it must be admitted that during the years from 1925 to 1940 when specialists were getting their start here, the general men with whom they were competing had received almost no hospital training. The young general practitioner of today with two or three years of well balanced hospital training behind him can offer a very different brand of competition from that of the practitioner of 1930.

What are the faults in this set up? There are occasions, perhaps not too rare, when a family of five will be under treatment by three or more physicians simultaneously. During an epidemic of respiratory infection the pediatrician on his rounds may enter a house just as the internist or otolaryngologist is leaving. A family has a handful of separate bills at the the first of the month instead of a single one.

Twice in the past three years an attempt has been made in the Lynchburg Academy of Medicine to organize a panel of physicians to answer emergency night and weekend calls. The discussions probably served a purpose in making each man realize his responsibility to make definite arrangements to cover his practice while away, but they failed to set up a panel. Too few men were willing to take all types of calls.

We all agree that it will be most interesting to observe the course of practice during the next few years.

THE CHANGING PRACTICE OF PEDIATRICS*

By HAROLD D. LYNCH, M.D.
Evansville, Ind.

THERE is an increasing awareness on the part of pediatricians of the importance of the psychiatric aspects of our specialty.

Realization that the child has emotional and social aspects to his existence has come to us slowly and has caught those of us trained chiefly in the anatomic phases of medicine in a state of unpreparedness and uncertainty. The revolutionary change which is taking place in pediatric practice creates real confusion when an attempt is made to define the

* President's address at the Annual Meeting of the Indiana State Pediatrics Society held at the University of Indiana Medical School, Indianapolis, April 23, 1952.

actual scope of pediatrics. If we, as pediatricians, have difficulty defining our specialty, it is not surprising that physicians outside our field have an extremely vague idea of the functions of the pediatrician.

The internist and the general practitioner, when asked what pediatrics means to them, typically reflect the general impression that it is child care with the confining age limits of from 6 weeks to 6 years, and that possibly this brief span could be absorbed by those not limiting their practice to a certain age group. This concept, which is not entirely unreasonable, is more widely held than we might like to admit. The obstetrician may feel that he can take care of the newborn as well as we; the general practitioner may believe that he can do as good a job with measles and other contagious diseases, and the internist certainly has a similar notion about heart diseases and blood dyscrasias.

It is pertinent and timely for us to take heed of the insidious but drastic changes in the practice of pediatrics over the past decade. In former years the pediatrician's chief function was to clear the hurdles of the first few years of life with proper feeding methods, to prevent or modify the dangerous episodes of the contagious diseases and the gastrointestinal maladies. Of necessity, he was so absorbed in the problems of the child's survival that little attention was given to his existence between these acute and dramatic episodes. In fact, there was no problem of growing up unless such obstacles were removed. Now that so many of these mountains have become molehills, we can get a clearer longitudinal perspective of the child's path of development. This over-all view reveals a necessity for attention to the psychiatric phases of the child's existence.

Failure to assume these new responsibilities seriously limits our influence. Thus limited, the impressions of some of our medical colleagues have some basis in fact: We feed the infant through the first year and then have a tendency to forget his nutritional problems. He is immunized against diphtheria, tetanus and pertussis, leaving only the occasional booster to be given during the runabout years. In the first school years comes the flurry of contagious diseases and bouts of upper respiratory infections which may give the child contact with the pediatrician for another short time. After this period of the early school years, in which the child builds a relative immunity to most of the common ailments, we lose contact with him entirely. He doesn't get "sick" any more. Then comes adolescence. He does not want to return to the baby doctor. As a result of the interruption of continuity, the pediatrician's influence may be abruptly terminated shortly after infancy or at any one of a number of points prior to adolescence.

If we wish to direct the care of the child from birth through adolescence, we must supply these missing links in the child's physical domain and incorporate many facets of the child's development which might be considered to be in the realm of psychiatry. To achieve this we must have regularity and continuity of supervision.

The question arises, how can this be done? How can our physical supervision, which now lacks continuity, be combined with psychologic guidance to form a program of complete child care? It appears to me that the one strong link which is necessary to weld the loose ends together is a vigilant and uninterrupted supervision of the child's nutritional status.

No other segment of pediatric supervision has as much to do with child health as nutrition. This basic truth has escaped us, leaving the public, whose interest in nutrition is insatiable, to get its information from sources outside the profession.

Misconceptions prevail. Experimental data of a fragmentary nature in the form of advertising copy on childhood nutrition has been directed at the laity. Foods of demon-

strable value to the laboratory animal or to the child, for brief experimental periods, are purported to be good for the child throughout his long developmental span. There is a dearth of longitudinal clinical studies to confirm many of the nutritional dogmas created in this manner. Our uncritical and passive assent to "spoon-fed" data has played no small part in the prevalence of nutritional misconceptions. Fads and fancies concerning the child's needs and how to get essential substances into him has produced an amazingly prevalent phenomenon: "My Child Won't Eat." This, the commonest complaint heard in the pediatrician's office, is almost invariably accompanied by some degree of malnutrition; malnutrition in the land of plenty and in a country having "superlative" medical care! Competent and complete pediatric care cannot be consummated as long as we persist in ignoring this challenge.

While the contributions of sound nutritional guidance to the physical welfare of the child are obvious, the psychiatric aspects of nutrition may be even more important. Problems arising from the feeding process penetrate deeply into the emotional, social and intellectual phases of the child's development. We are prone to forget that eating, for the human (and the child *is* human), is a social and emotional experience. During the first year, the infant's rapid rate of growth, and his eagerness and need for food, are a joy for all concerned. He steadily gains weight, as shown by his monthly trips to the doctor's scales. The feeding problem is irreducibly simple in these early stages. Like nutrition in animals, it depends almost entirely on the availability of food.

Shortly after the first year, the psychiatric aspect of nutrition rears its ugly head. The rate of growth of this voracious yearling has dropped sharply. As a result, he is not interested in food; there are many other things to do and to learn. The baby no longer has the proper respect for his "vegetables" and his "calcium." On the other hand, the family's interest in poking these substances into him has not waned. The fun of feeding him has changed to a serious problem. All the family, and some of the neighbors, eventually get into the act. Soon he is bribed, forced, entertained and browbeaten. Conflicts from the lack of understanding of a simple physiologic fact in nutrition may spill over into other fields of behavior, such as bowel and bladder control, sleeping habits, etc. The life of the runabout is made difficult.

Later, at the school age level, an uninterrupted program on nutrition can help prevent the common practice of letting the child live on a diet of highly refined carbohydrates, which usually leads to dental caries, anemia and poor tissue turgor. Naturally he is tired, irritable and otherwise emotionally disturbed. He doesn't get along in school, or with the teacher or parents. The urgent need is to correct his underlying malnutrition rather than to give him a tonic or to add fluorine to his drinking water.

An even greater magnification of these mental and emotional and social difficulties, stemming directly from poor nutrition, is more apparent when the child reaches the unstable and uncertain period of adolescence.

Continuity of care, fostered by nutritional supervision, gives the pediatrician leverage not otherwise obtainable in all aspects of child development.

To summarize: Adequate nutrition is the keystone in all respects of the child's growth and development. Effective supervision of nutritional problems will serve to consolidate our various fields of influence. It will encourage uninterrupted supervision of the child and will bring comprehensive pediatrics closer to reality. Achievement of this goal is necessary if we wish the laity and our medical colleagues to stop looking upon us as "baby doctors."

In our desire to embrace many of the psychiatric aspects of pediatrics, we must realize that there is a zone between pediatrics and psychiatry through which our equipment will not permit us to venture.

The specialty of pediatrics is a young one. It is undergoing changes and turmoil so that in reality, the specialty itself is in its adolescence. All of us practicing this specialty must learn the psychologic approach, but let us admonish ourselves not to contribute to the "pimples" of this adolescent branch of medicine by becoming amateur psychiatrists.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

IT APPEARS timely to call attention again to the work and objectives of the United Nations International Children's Emergency Fund. Particularly noteworthy is the trend to use this fund more and more in efforts to help other nations help themselves. Thus the mass attack on tuberculosis, yaws and malaria are, it is hoped, bringing those diseases into proportions where their continued control can be more effectively managed. Similarly, increasing attention is being given to the training of professional and technical personnel.

The plans and long-range purpose of the UNICEF have recently been described by Maurice Pate, Executive Director of the fund[1]:

"Five years ago, in May 1947, the United Nations International Children's Emergency Fund received its first pledge of support, a contribution of $15,000,000 from the United States Government. A number of other pledges and contributions soon followed, and procurement of supplies was begun. By the middle of 1948, those supplies were reaching several million children.

"Those early beginnings were in the minds of many of us at the recent meeting of the Fund's 26-nation Executive Board (April 22-24), for on that occasion UNICEF's aid was extended to the only remaining area of need in which it had not been operating—Africa, south of the Sahara.

"In the Belgian Congo, French Equatorial Africa, Liberia, Togoland, the Cameroons and West Africa, UNICEF, side by side with the World Health Organization and the Food and Agriculture Organization, will soon be working with the governments and people on a number of child-health projects. The largest of these is to be an attack on kwashiokor, a dietary deficiency disease that affects thousands of young children in these regions. Smaller projects are for malaria and yaws control, not on the mass scale that has been possible in some of the other areas, but important, nevertheless, for out of such small beginnings the larger effort follows.

"*Scope of the Work.* Europe, Asia, Latin America, the countries of the Eastern Mediterranean, and now Africa. That has been the order, and by the time the new UNICEF-assisted programs are in operation, help will be going to 72 countries and territories. That help has come from nearly 100 countries and territories, the equivalent of $166,000,000 having been raised.

"If this global operation is described in terms of children, their numbers are interestingly large in proportion to the sums expended. Take only one operation, the BCG anti-tuberculosis campaign, begun with the help of the Scandinavian countries and UNICEF and now carried on in three continents with the help of UNICEF and WHO. In Europe alone, from 1948 through 1951, 16,000,000 children were reached, of whom 8,600,000

[1] Pate, Maurice, Plans of Children's Fund and Their Long-Range Purpose, United Nations Bulletin, vol. 12, No. 10, May 15, 1952.

were vaccinated. Millions more were reached in the North African and Eastern Mediterranean countries and in Ecuador, Mexico, India, Pakistan, Ceylon, Malaya, and Singapore, a combined total of nearly 10,000,000 were tested and over 4,000,000 vaccinated. The corresponding figure for those campaigns currently being assisted, that is, those for which aid is being given by UNICEF and WHO, is over 50,000,000. That is the number to be tuberculin tested, to find those in need of vaccination. The second step is the vaccination itself, which will involve from thirty to fifty per cent of those children, depending upon their age and the areas where they live.

"The totals for other of the UNICEF-WHO-assisted campaigns likewise run into many millions. Currently-assisted campaigns against yaws, bejel, and syphilis, in Asia, the Eastern Mediterranean, and Latin America are expected to reach 23,000,000 persons. That number will be examined, and all found to be infected will be treated with penicillin. The insect-control campaigns, against malaria, typhus, and other diseases, will reach nearly 20,000,000. In addition, various immunization programs will reach 1,250,000, and other miscellaneous projects some 3,700,000. The numbers cannot be totalled, for the same child may benefit from more than one of these programs.

"*Feeding Children.* The numbers around the 'UNICEF food table,' figuratively speaking, are now relatively smaller, considering the far greater numbers who were there in those first years. In the spring of 1950, in Europe alone, as many as 6,000,000 children were receiving an 'extra' meal, with the help of UNICEF. Mass feeding, as such, has not had a place of importance in the Fund's operations outside the original war-ravaged countries of Europe, but even so there are still emergencies to be met in various areas. More than 400,000 children are being aided among the Arab refugees; 100,000 in the drought-stricken area of Brazil; 75,000 in the drought-stricken state of Madras, India.

"Also UNICEF has been assisting some large-scale demonstrations in school feeding. This type of UNICEF aid is of main importance now because of the way it is being used to raise the nutritional levels of the assisted countries. The outstanding example is the development that is taking place in the Central American countries. There, milk from UNICEF, as well as margarine and vitamins, has been used to establish child-feeding programs in schools, nurseries, and other centres. Those programs are being built so that the countries themselves can take over the entire responsibility and continue them on a permanent basis. Already, these countries have increased their expenditure more than tenfold, from a total of approximately $50,000 prior to the initiation of the UNICEF-assisted programs to the present outlay of nearly $500,000.

"These figures serve as only one measure of the effectiveness of this United Nations operation. Another, and perhaps even more important one, is not now calculable, for its results lie altogether in the future. Its success will be measured by the extent to which the countries now receiving this assistance are able to take care of their own needs, for it is to that purpose that UNICEF's efforts are now being made.

"*Long-Range Plan.* All that UNICEF is now doing, with the exception of the help offered in emergencies, is for the long-range purpose. The large-scale campaigns against tuberculosis, yaws, malaria, and other diseases that have been described are part of that effort, for by this mass attack, it is hoped, those diseases can be reduced to manageable proportions. There is, for instance, no possibility now or in the foreseeable future of dealing with tuberculosis by the common control methods of isolation and hospitalization. The numbers affected are far too large; facilities are all too few, or practically nonexistent; and the number of doctors and nurses is altogether inadequate. The oncoming

generation, however, can receive a measure of protection by vaccination, at a relatively small cost, and countries generally can find and train the personnel needed for carrying out the work. UNICEF assistance is being given now in such a way as to make it possible for the countries to keep up the work on their own

"Likewise, yaws, a disease affecting millions of children in certain tropical areas, can be dealt with, because the method—treatment with penicillin—is relatively simple and inexpensive. Nontechnical people can be trained for the work, and the organization of the campaign is within the countries' means. Each yaws case cured is a source of infection gone, so that it now seems possible, in five years' time or so, to have so reduced the number of cases that they can be speedily dealt with by the community.

"So with malaria and other insect-borne diseases: after only one spraying, a community is protected. New cases are a rarity. The problem, then, is to continue the spraying, from season to season, and to that end UNICEF is supplying the DDT, sprayers, jeeps, and other equipment for the short run, while the countries get ready to take over. In some instances, UNICEF is providing equipment for DDT manufacture: this help is given only in special circumstances, namely, where the need warrants the effort, and where essential materials are on hand to make local production practicable.

"*A Service Network.* Hand in hand with these campaigns goes the unspectacular work of building a network of services—centres where people can go to get help in taking care of their children. They are modest places, for the most part, sometimes makeshift arrangements in the back of a school-room, or in a church or a temple; but they serve the purpose well until a better place is possible. UNICEF provides the scales, thermometers, and other essential equipment not otherwise available. The government, or the community itself, provides the rest. Nearly 1000 of these centres are being equipped in Asia; over 800 more will receive equipment as a result of the last Board session.

"Already, women are coming to these centres regularly on the day when the doctor or the nurse or the nurse-midwife, is there. Their babies are weighed and examined, and they are told what to do to keep them well. If the babies are sick, the mothers are given some simple medicines for them. In some instances, there is milk—powdered skim milk—for the children and for the women during their pregnancy and nursing period. Dr. Martha M. Eliot, Chief of the United States Children's Bureau speaking before the Fund's Program Committee, likened what is being done to what was done in the United States a generation or more ago, in getting services started. 'Milk stations' were the first step, that is, places where mothers could receive safe, wholesome milk for their babies, free or at low cost. The milk, valuable in itself, also served as an inducement to get mothers to the centres. Once the contact was made, and confidence gained, the mothers could be enlisted in the larger health program.

"So now with UNICEF: the milk, the cake of soap, the medicine, and other 'expendables' which it is providing for these new centres are an attraction. And, as these centres become an accepted part of the community, they will be able to take over the continuing responsibility for the general health. Their own staffs will do the vaccinating; they will watch for new yaws cases and treat them. Above all, they will quicken the community's interest in dealing with its own health problem, of which environmental sanitation is so important a part. There is much communities can do, without outside help, once the people realize the importance to them and their children of these control measures.

"They are learning. The yaws campaigns are an example. The results are so dramatic

and convincing—a cure after only one or two injections of penicillin—that the people are ready to act upon any other advice 'the health people' have to give them. They also take matters into their own hands, as illustrated by a report from Thailand. There, the villagers who have been reached in the yaws campaign have a stern discipline. Anyone coming into the village who has yaws—and the villagers know its signs—must first be treated before he can settle among them. Often a treatment centre is a considerable distance away, and must be reached on foot, but the rule is the rule.

"*Problems of Training.* Hindering all these efforts to get services to the children is the lack of trained men and women, especially for work in the rural areas. UNICEF, as a matter of policy, is encouraging training efforts, but training courses are still too few. New ways have to be found of recruiting and training people for this work, for the old ways will not do. At the present rate of recruitment and training, in respect to one key group, midwives, it would take some countries fifty or more years to train the number needed. In a few countries, though, this problem is beginning to be faced, as was brought out in the Executive Board meetings.

"Brazil, for one, is providing short-term midwifery training, three or four months, for locally-selected women and girls. These candidates are sent for training to nearby centres, in communities not too different from their own. Their expenses are paid by their communities, with the understanding that, on completion of their training, they will return. UNICEF is helping to equip the training centres for these girls. It is also providing midwifery kits for use while the girl is training and, later, in her community practice. The kit, from the United Nations, is her diploma. She returns to her village sure of a job—a community can just as easily support a trained midwife as an untrained one, and it has always supported the latter. She has standing; and, most important, she is not 'overtrained,' and, in consequence, unwilling to work in the village.

"Haiti, to cite still another instance of how a country is solving a problem of getting people for the work, is using jeep-drivers, skilled and deft with their hands, to give the penicillin injections in its yaws campaigns. Dr. Sasha Levitan, of the World Health Organization, who directed that very successful effort, when faced with a shortage of medical technicians, decided that a man who could skillfully handle a jeep could conceivably be taught to stick a needle into a person's thigh, as directed. So now, the driver of the jeep from UNICEF gets to the village, sets up office as it were, treats the yaws cases, one after the other, and moves on to the next village.

"India, too, is fitting the training to the need, in its plan for extending the UNICEP/WHO-assisted vaccination programs. It is recruiting and training 'lay vaccinators' to travel as teams throughout the countryside, and it hopes to have 100 teams by 1953. Each team can test 100,000 children a year; 100 teams, 10,000,000.

"To all these schemes, UNICEF is lending its support, with the hope that as they prove successful in one country they will be followed in others. The one thing certain is that some way must be found to get men and women for these fundamental tasks for, failing to do so, the present conditions of poverty, ignorance, and poor health will perpetuate themselves.

"The will is there to do something now, a will made evident not only in the requests that are coming in for UNICEF aid, but as that aid is to be used in connection with other help offered by the United Nations and its specialized agencies. The main responsibility, though, rests with the governments and the people themselves. UNICEF's records, as well as those of the other international organizations, carry on the other side of the ledger

the far, far larger sacrifice and contributions of what the assisted countries themselves are doing.

"*Current Projects.* The sum being asked by UNICEF for the coming twelve months' period is a modest one, only $20,000,000. It is not likely, in view of the demonstrated usefulness of the Children's Fund, that the governments and the people, will fail to raise that $20,000,000.

"A break-down of the projects to be furthered, as a result of the last Executive Board's action, is given here by geographical area:

Africa (exclusive of Eastern Mediterranean countries), $1,000,000.
Asia—$2,203,000.
Eastern Mediterranean—$637,000
Europe—$970,000
Latin America—$857,000
Emergency Situations—$2,299,000."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

Steadily increasing use of the laboratory in clinical medicine and the present-day tendency of the clinician to place great reliance on public and private laboratories prompted the editor of this column to invite Dr. Albert V. Hardy, Director of Laboratories, Florida State Department of Health, to write the accompanying article. The difficulties which he points out are real and the experience which he has had in promoting improvement in the performance of the laboratories in Florida is encouraging. Extension of such improvement in laboratory performance is a direct concern of every pediatrician.

RELIABILITY OF LABORATORY FINDINGS

By ALBERT V. HARDY, M.D., DR. P.H.

THERE are admitted limitations in our clinical examinations. The history may be biased. Significant departures from the normal may not be revealed by expert inspection, palpation and auscultation. Even x-ray is of help only when tissues of varying density are involved. Hence more and more we have turned to the laboratory for reliable data. It is to the great credit of the laboratories that in our teaching centers the results have had that degree of reliability which developed in our students a feeling of complete confidence in reported laboratory findings. It is not our intention to question whether this degree of confidence was warranted, but it is our purpose to make some observations on the reliability of laboratory examinations available to most of us in the practice of our profession. If laboratory findings are not as reliable as we expect them to be, can they be made so?

"A Survey of the Accuracy of Chemical Analyses in Clinical Laboratories" by Belk and Sunderman[1] has been quoted repeatedly. The Pennsylvania State Medical Society sponsored the study. The 59 laboratories which voluntarily participated were under the direction of pathologists and chiefly in hospitals. The quality of work of small laboratories operated by a technologist or performed by individual technicians in physicians' offices was not assessed. The findings, it is presumed, are the more favorable observations for laboratories of one state.

Samples for check-testing were submitted to the participating laboratories and results were reported and evaluated without identification of the laboratory concerned. To illustrate, a glucose solution with 60 mg. of glucose per 100 cc. was submitted, the result was considered satisfactory if readings were within the range of 50 to 70 mg. Of the 52 examinations reported, 33 were satisfactory. But the range of unreliability varied from under 40 mg. to over 300 mg. Considering all tests, less than one half of the results were considered satisfactory, and there were 105 "gross errors" in the 585 results reported.

In the field of syphilis serology, Hardy[2] has reported on the "Reliability of Serologic Examinations as Performed in Medical Laboratories in Florida." Series of specimens were submitted for examination to 105 participating laboratories. The findings were compared with those of three "Control Laboratories." The quality of performance was graded ob-

jectively and classed as excellent, satisfactory or poor to highly unreliable. On the first series of specimens the laboratories were graded according to performance as 30% excellent, 36% satisfactory and 34% poor to highly unreliable. There was substantial improvement in the second series. The third series was submitted six months after the first and at that time the laboratories were graded according to performance as 67% excellent, 27% satisfactory and 6% poor (with none highly unreliable). The author was of the opinion that a major factor in rapidly attaining this degree of improvement was the stimulus provided by the evaluations. There was however a concurrent educational program which included distributing to all laboratories copies of standard test procedures. A consultant also was made available to all laboratories desiring assistance. The brief report concludes, "Methods which have proved so effective in improving the quality of performance in serologic work could, with advantage, be applied to other technical procedures."

The problems are not limited to clinical chemistry and serology. The malariologist will attest that many of the cases of malaria being reported currently in the United States are the result of erroneous positive laboratory reports. How exact are the simple procedures in hematology, in the hands of the expert and as done by the poorly trained, relatively unsupervised and overworked technician? Basal metabolism findings on the same individual may fluctuate widely. Is this the result of changes in the individual or of defects in technics?

The pathologists in Pennsylvania through a questionnaire expressed their opinions as to the factors contributing to the technical inaccuracies revealed in the study of Belk and Sunderman. The poor training and inadequate number of technicians was considered of major importance while inadequacies in space and equipment were serious contributing handicaps. Warren Sperry, Associate Professor of Biochemistry, Columbia University, comments[3] that defects might be expected since clinical chemistry is "a weak, undernourished, underdeveloped, handicapped child." He further observes, "If the findings published by Belk and Sunderman are typical, and we have no reason to say they are not, they must be a matter of deep concern, both to the chemical and medical professions."

There are notable differences between pediatrics and the medical laboratory field. All pediatricians are physicians, a homogenous and relatively harmonious group. Assistants may be relied upon for specific duties, but medical histories and physical examinations are done by the pediatrician himself. In contrast, a variety of persons, medical and nonmedical, are concerned with the laboratory field. Even if a pathologist or other physician is in charge of the laboratory, the nonmedical worker does most of the tests, from the taking (or receiving) of the specimen to the preparation of the report. Among laboratory workers there is evidence of division rather than of unity. Internists and pathologists have a possessive interest in clinical pathology; the pathologists and the chemists both claim clinical chemistry. The technologists vary widely in training, have competing national organizations, and rarely any local group activity to unify, stimulate and educate. There are the differing activities and interests of the laboratory workers in hospitals, blood banks, physicians' offices and in public health. The private laboratories operated by technologists are seeking wider acceptance and fearing and bitterly fighting opposition. The public health laboratory, since it provides free service, is regarded to varying degrees as the unfair and unwanted competitor. These features of the medical laboratory field are enumerated in explanation. That weaknesses exist under these conditions is not surprising.

There appear to be several important conclusions from this situation. As has been

emphasized repeatedly in the medical education of most physicians accurate diagnosis requires a summation and integration of all the data about a patient. It is a mistake to rely solely on any one source of information, the laboratory included. Even under the best of circumstances an occasional error is possible and the physician must not allow a blind faith in the laboratory to do his thinking for him.

On the other hand, modern medicine inevitably leans heavily on the laboratory to supply essential information. It thus becomes a vital consideration for all physicians to encourage continual raising of standards for public and private laboratories. There needs to be more recognition of the laboratory technician on whose knowledge, skill and integrity the accuracy of the work depends. Facilities for training laboratory technicians need further support. Some of the schools for laboratory technicians need to raise their standards and improve instruction and supervision.

It is logical that the public, tax-supported laboratory should consider as one of its important functions the setting of standards and the raising of the level of general laboratory performance in the community. This involves educational as well as investigational activities, for which personnel and funds are not always available. The improvement in reliability of serologic tests in Florida was effected through the participation of the State Public Health Laboratory. Similar voluntary cooperative activities in other fields appear promising and warrant trial.

References

1. Belk, W. P., and Sunderman, F. W., Study of accuracy of chemical analyses in clinical laboratories, Am. J. Clin. Path. **17**:853, 1947.
2. Hardy, A. V., Reliability of serologic examinations as performed in medical laboratories in Florida, J. Florida M. A. **36**:427, 1950.
3. Sperry, W. M., Professional status of clinical chemistry, Chem. Engineers News **28**:159, 1950.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

USE AND ABUSE OF NEWER KNOWLEDGE OF GROWTH AND DEVELOPMENT IN SCHOOLS

By ALFRED YANKAUER, M.D., M.P.H.*
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THE impetus to learn more about child growth and development was stimulated by the White House Conference of 1930. Knowledge has advanced tremendously in recent years and is supported by a voluminous literature dealing with special phases of the process. In a few places the results of an interdisciplinary approach to longitudinal studies over long time periods are beginning to be correlated. Although much still remains unknown, certain positive principles have been discovered which urgently call for extended application if today's schools are to help rear the healthy, productive citizens of tomorrow.

Three major principles characterize this newer knowledge—principles which apply equally well to growth and development expressed in terms of body chemistry or in terms of interpersonal relationships. The first is that healthy growth progresses naturally and regularly according to general patterns and stages that are characteristic of human experience. The infant is not a miniature child, nor the school child a miniature adult. This may seem obvious, yet it was only a few years ago that infants were started at toilet training long before they had reached a phase of development that rendered them capable of controlling the neuro-muscular apparatus of elimination. Even today there are many people dealing with school children who believe that "character" is formed by habits of thought, authoritatively conditioned, rather than by the constructive resolution of problems met in specific stages of total development.

The second principle is that within this general pattern of human experience each individual charts his own unique course, a course consistent for himself but differing from those of his peers. An analogy may be made with fingerprints which conform to a general pattern for all human beings yet differ so significantly that they may be used for identification purposes. This may seem obvious also, yet it is far from appreciated. Large numbers of parents are puzzled and worried when their 15 month old shows no interest in walking. Schools are still sending notes home to parents informing them that their children are 5 to 10% "underweight" and faithfully recording the information in their records.

The third principle is that all aspects of growth, physical, intellectual, emotional, social, and all the descriptive adjectives that can be applied—all aspects are interdependent and interrelated in more ways than we can begin to understand. Yet it was not too long ago

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that convalescent homes and open-air classes flourished in our communities and schools. In general they operated under the well-meaning but misdirected notion that growth failures could be treated by temporary modifications of regime without much attention to underlying causes. Often temporary physical improvement resulted, but the gains were soon lost when the child returned to his former unchanged environment. Many of our schools today accept results of current intelligence tests as reflecting innate abilities incapable of growth, although we know that such results may reflect only distinctions of caste and class or emotional climate.

These three principles, the pattern-formation, the uniqueness, and the interrelationship of the growth process, will be discussed as they apply to school personnel, program and technics.

School Personnel

Three areas of application to personnel working with school children suggest themselves. The first involves recruitment and selection. If the successful nurture of true learning—learning to meet and solve problems in a real world—is closely related to building successful relationships with people, every adult to whom a child relates in school must be a warm, insightful, and real person. This is perhaps the most important single implication that can be made from all our knowledge; for programs and technics are no better than the people who manage them; and, if there are not enough people to manage, the best programs will fail. It is also the most frustrating implication; first, because our technics of selection are not yet good enough to select this kind of person from among those who look to teaching, nursing or counselling as a career; and second, because even if they were that good, the prestige and financial rewards of such careers do not attract as many persons of this caliber as they should. Here lies the most serious lag between the acquisition and application of knowledge in our entire civilization. Its importance cannot be emphasized enough, and it is the duty of all who work with children to take every opportunity to bring it before the public.

The second area involves the training of personnel who work with school children. Knowledge of children would seem to be as important as knowledge of subject matter in the preparation of such personnel for their careers. That physical abilities and physical form, ways of behavior and centers of motivation, progress through definable stages, are facts which can be taught. It is hard to believe that anyone working with children for any length of time has not already absorbed some such knowledge empirically. The problem is to get such knowledge to them before they assume responsibilities, and to make such knowledge meaningful so that they will not assume, for example, that the fighting or sloppiness of a 9 or 10 year old is a sign that the world is going to the dogs.

The third area involves specialization of personnel working with school children, an area in which our newer knowledge has led, unfortunately, to growing confusion. Scientific discoveries and specialization have always gone hand in hand. Industrial output has increased coincident with the development of assembly-line technics. But apply specialization to education, and the single teacher in a one-room school-house becomes split into a multitude: health and physical education teachers, nurses, vocational and guidance counsellors, psychologists, social workers, and even health coordinators. In the shuffle we may sometimes lose the child. Obviously a return to the one-room school house is no more desirable than a return to the horse and buggy doctor, who, although he may have rendered total service, nevertheless rendered service based on horse and buggy knowledge. Staff conferences, school health councils, and integrated record systems are only a part

answer to the vexing question of how to bring all our knowledge and skills together to serve school children. Although specialists are needed in all schools, the increasing compartmentalization of responsibilities can be gravely abused. A more fundamental solution to the problem brings us back to our first point: the selection and training of more and better teachers who are prepared to assume many roles within the limits of their capabilities and who have small enough class units to permit them to do so. Under these circumstances the specialist would become a consultant rather than an individual to whom are shunted full responsibilities for all problems in his special area.

School Programs

To a large extent school programming has always been adapted to the needs and skills of a child at a given age. This has had to be true. A 10 year old can perform physical and mental acts which no amount of education could teach the 6 year old. Nevertheless real changes in curriculum content in accordance with the concept of a stage of readiness to learn have resulted from newer knowledge. A first grade child is no longer expected to recite the alphabet nor a third grader to write flawless script. More important than these considerations is the realization that learning to read and write are important buttresses to establishing a sense of autonomy and initiative at this stage of personality growth. These are examples of how curriculum can be and has been adapted to patterns of total child development.

Sometimes, however, the exigencies of our own culture (of which the school, after all, is only a part) make it impossible to apply the knowledge which we have acquired. The classroom over-accentuation of competitive drives and its warping effect on the development of some children is an example of this. The example can be extended to physical education and the athletic field where, in addition to psychologic hazards, physical hazards result from the introduction of a youngster to competitive athletics before he has completed his adolescent spurt of growth and development.

In addition to adapting itself to growth stages of learning readiness and adjusting its incentives year by year to the central motivating force in that year's sequence of personality development, the curriculum should be flexible enough to permit each child to express and develop his unique self. This necessity together with knowledge of the interrelationship of all growth has led to a change in the concept of the curriculum. What used to be thought of as specifications of subject matter to be covered each year has become the sum total of school experience.

Putting this concept into practice is not easy, partly for reasons that have already been touched on and partly because ways of doing so are still uncertain particularly at secondary school level. The extent to which they are actually practised is not known. Certainly there still remain many areas of education that can be brought together more closely, even with existing deficiencies of personnel and facilities. Health education and health services are a prime example. In how many schools is the administration of first aid to a pupil looked upon as a living, teaching experience in which the whole class can share, rather than as an annoying repair job for the nurse or clerk or teacher? How often are height and weight measurements done with assembly-line efficiency rather than with an understanding of the teaching opportunities they offer? Health appraisals by a family or school physician are as much a part of the school curriculum in its broad sense as the multiplication tables are in its narrow sense. Yet if only a fraction of the educational ingenuity expended on arithmetic were applied to making this contact with a physician interesting and meaningful, the experience could be tremendously vitalized. A real educational lag exists here. Although

educators may conceive of the curriculum as the sum total of school experience, they tend to leave the school health services out of this experience. This oversight probably arises from the fact that school health services began as a public health effort in a school setting rather than as part of the teaching services of the school. They have remained in this position in most minds even though many health services are administered by boards of education, and even though their original purposes—the control of communicable disease and the detection of early defects—are no longer valid enough to justify their continued existence on the same scale, as a public health effort alone. If school health services truly became a part of total school experience, however, their existence can be more than justified.

School Technics

Although many new technics have been developed to help teachers, psychologists and counsellors to better understand the total growth of children, technics varying from sociograms to surveys, only technics of measuring physical growth will be commented upon in this discussion.

It is clear that measurements of physical growth must be compared to standards of some sort in order to interpret their significance. The realization that each child grows along his own pathway to his own unique adulthood as well as the "concern with the doing and becoming of the organism more than with its status on any given day,"[1] has led to the development of technics which attempt to record the child's growth progress and measure it against itself as well as against that of others.

Stuart and Meredith have proposed that a series of six measurements be made periodically including chest and calf girth, hip width, and subcutaneous tissue, as well as height and weight.[2] These are to be matched against age-specific percentiles with the object not only of placing the child in relation to other children at this stage of growth but also of comparing him to himself by comparing his percentile placements at different stages of his own progress.

Unfortunately, no concrete evidence exists that could administratively justify a school health service in undertaking the extended effort and expense required to make such measurements routinely. The recording of the measurements is laborious and their interpretation cumbersome. Measuring physical growth on this scale must be considered a luxury service even though scientifically accurate.

Height and weight changes are the most consistent outer changes of body growth and have been studied the most intensively. They are simple to make and of interest to the children whose growth progress they measure. Graphic methods of portrayal facilitate their interpretation.

Two principal graphic methods are in current use. Meredith has prepared a "Physical Growth Record" with separate height and weight graphs plotted by age for boys and girls.[3] This may be obtained through the American Medical Association. The record may be reproduced by schools who request permission to do so. Five continuous normative zones are blocked out on the graphs. Zone location for height and weight may describe inherent physique or a bodily deviation due to other causes. The relationship of the individual's plotted curve for height or weight to his normative curve over a period of time affords some information about the satisfactoriness of height and weight growth. The data on which these graphs were based was obtained from measurements of white children of northwest European ancestry living under better than average conditions over a period from 1930-1945.

Wetzel has devised and copyrighted a "Grid for Evaluating Physical Fitness."[4] This is sold to schools and other customers by the Newspaper Enterprise Association Inc. of Cleveland, Ohio, the "World's Greatest Newspaper Feature Service." The grid consists of two graphic sections. In one section height on a horizontal arithmetic scale is plotted against weight on a vertical logarithmetic scale. This section is traversed obliquely by a set of "channel lines" intended to describe physique. A set of "iso-developmental lines," intended to describe body size cuts across the channel lines at regular intervals. The second section plots the body size obtained from the first section against chronologic age and is obliquely traversed by "auxodrome" lines intended to describe schedules of total development. Channel of location in the first section may describe physique or bodily deviations due to other causes. The path of the plotted curve in relation to channel lines in the first section and to auxodrome lines in the second section affords some information about the satisfactoriness of total growth. The slope of the channel lines and "auxodrome" lines and the calibration of the "iso-developmental lines" have been derived from mathematical formulae based on the characteristics of the growth process in which various sets of measurements of human growth were substituted to derive the specific mathematical constants. Because the combination of two measurements (height and weight) is related mathematically, the grid describes the mass phenomenon of body growth with constancy. However, it fails to distinguish between the bone, muscle, fluid or fat which may make up differing proportions of the mass. These qualities can only be evaluated by some method such as that proposed by Stuart and Meredith or by even more complex technics.

In a school health program there are several important applications of the practice of weighing and measuring children routinely. Their value as a part of the health education program has already been commented upon. Either one of the graphic methods discussed is unquestionably more useful educationally than previous methods of recording height and weight measurements. Children are literally able to watch themselves grow and this can be used to heighten their interest generally or to center their interest if they are obese or definitely below-par clinically.

There can be no question that either of these dynamic methods of portraying growth are more helpful to the family or school physician when he makes his total health appraisal of the school child than previous methods. Static weight for height and age tables are considered virtually worthless at the present time.

School health services are constantly seeking efficient and economic methods to differentiate between the healthy and the unhealthy among the mass of children they serve. The Wetzel grid has been proposed as a simple method of accomplishing this goal with a high degree of accuracy.[5,6] It is claimed that children whose measurements place them in lower physique channels or lower auxodromes and children whose plotted lines drift from one channel or auxodrome to another over a period of time belong in the unhealthy group whereas children whose plotted lines follow a consistent channel and auxodrome (other than extreme upper and lower) can be considered healthy.

Since there have been no objective studies of the over-all incidence of major health problems among a group of school children as related to the normality or abnormality of their grid patterns, this claim can neither be proved nor disproved. However, when the fundamental assumptions underlying it are critically analyzed the claim itself seems excessive.

The presence of a child in the lower physique channels either at one reading or consistently over a period of time does not necessarily connote inferior nutritional or health

status. As a matter of fact evidence exists to indicate that the thin-framed individual is healthier and lives longer than the average individual.[7] Some of the children in the lower physique channels are there because of poor nutritional status but not all of them.

The drift of a child's growth curve from one channel to another over a time period unquestionably means something, because the mathematical relationship of height and weight in the grid is such that it expresses something constant about the total growth process. However, we are far from being able to interpret what the drift means in many cases.[8] Furthermore we are not certain that groups of children in actual nutritive failure have significantly more drifting from channel to channel than well-nourished children.[9,10] Both this and the previous point have important implications. One of the reasons for the general disrepute of school health services is the number of ill-advised services and importunate referrals for medical care which they have made in the past. Perpetuation of such a pattern is not to be desired. If the channel drift of a child's grid pattern is to be used in conjunction with social and medical appraisal, it may serve a useful function although the extent of its contribution to the total school health service cannot be estimated at this time. However, if it is used without sound clinical judgment, more harm than good may be anticipated.

It is assumed that the consistent presence of a child in any physique channel except the extreme ones indicates that his growth and nutrition are satisfactory. The statistical probability of this assumption being true in any given case has not been computed. Perhaps it is fairly high, but it certainly is not 100%. Even more important is the really great danger inherent in assuming that all children who stay in their channels of growth are necessarily free from illness or disability. Major physical or mental disease must certainly exist without affecting the physical growth process as expressed by the grid. This has been demonstrated in the case of congenital heart disease.[11] It must be true in many other conditions as well.

Studies are badly needed at the present time comparable to those reported by Souther, Eliot and Jenss in 1939 but on a more extended scale.[12] These investigators compared four indices used in judging physical fitness against each other and against the judgment of a physician. Results were disappointing. If we are ever to improve the efficiency and quality of school health services we must have objective evidence to go on rather than data accumulated by individuals desiring to sell a particular product or idea.

Present technics of interpreting bodily growth are far better and more useful than former methods. They can play a constructive role within the established framework of the school health program. However, their role should be considered supplemental to the educational aspects of the program and helpful to the physician's appraisal. Their place in the screening aspects of the program must still be regarded as in an experimental stage. To quote one of the foremost students of child growth and development in the United States, "we have, I believe, only barely scratched the surface in gaining an understanding of those clues which should tell us of trouble in the offing if nothing is done to correct the situation."[1]

Summary

Present knowledge of child growth and development hinges around three general principles: the pattern-formation or stage, the individual uniqueness, and the interrelationship of all aspects of the growth process.

If we are to apply these principles to school children we need to recruit and select bet-

ter personnel to work with them; we need to bring the benefits of this knowledge to such personnel in their training; we need to break down the tendency to compartmentalization of such personnel in their daily work with children.

If we are to apply these principles to a school program we need to knit all aspects of that program together more closely than ever before. This is particularly true of the relationship of school health services to the school curriculum.

Technics of measuring physical growth have been devised which are superior to former technics. Although they have a useful, if limited, role to play in the total school health program, their role in the screening and assessment aspects of the program remains in an experimental stage.

References

1. Washburn, A. H., Pediatric Potpourri, PEDIATRICS **8**:299, 1951.
2. Stuart, H. C., and Meredith, H. V., Use of body measurements in school health program, Am. J. Pub. Health **36**:1365, 1946; **37**:1435, 1947.
3. Meredith, H. V., Physical growth record for use in elementary and high schools, Am. J. Pub. Health **39**:878, 1949.
4. Wetzel, N. C., in Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, vol. 1.
5. Wetzel, N. C., Simultaneous screening and assessment of school children, J. Health & Phys. Ed. **13**:576, 1942.
6. Wetzel, N. C., Role of grid technique in physical fitness program, M. Woman's J. **55**:19, 1948.
7. Armstrong, D. B., Dublin, L. I., Wheatley, G. M., and Macks, H. H., Obesity and its relation to health and disease, J. A. M. A. **147**:1007, 1951.
8. Stuart, H. C., How can we apply our knowledge of child growth and development? Child **16**:61, 1951.
9. Mann, A. W., Dreizen, S., and Spies, T. D., Determination of status and progress in children with nutritive failure, J. Pediat. **31**:161, 1947.
10. Mann, A. W., Dreizen, S., Pyle, S. I., and Spies, T. D., Red graph and Wetzel grid as methods of determining symmetry of status and progress during growth, J. Pediat. **32**:137, 1948.
11. Richards, Mary R., Growth patterns in congenital heart disease as shown by Wetzel grid, PEDIATRICS **9**:77, 1952.
12. Souther, S. P., Eliot, M. M., and Jenss, R. M., Comparison of indices used in judging physical fitness of school children, Am. J. Pub. Health **29**:434, 1939.

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INTERNATIONAL NEWS

NEWS FROM ENGLAND

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CENTENARY OF "GREAT ORMOND STREET"

The first patient was admitted to The Hospital for Sick Children, Great Ormond Street, London in 1852. Notice the capital "T." It has been said that all who have ever worked at this hospital are touched thereafter with a certain arrogance and hence the "T." It is believed that this was the first children's hospital in Great Britain to provide both for outpatients and inpatients. Up to 1852 there had been "dispensaries" for sick children, but the fear of infection and the devastating results when young children were herded together had prevented any development of inpatient facilities. The general hospitals excluded children. They died at home in large numbers. All this was changed by Dr. Charles West. He was an obstetrician on the staff of the Middlesex Hospital where he gave the lectures on diseases of children to the students—a common practice in those days. These lectures were collected into a book—"Lectures on the Diseases of Infancy and Childhood"—published in 1848 and running into several editions in Great Britain and in the United States of America. West had studied in Dublin where he noted the decreased neonatal mortality when certain hygienic measures were introduced and he had travelled in Europe and seen children's hospitals there.

Working at a dispensary for children south of the River Thames West failed to persuade the governors to extend the facilities there to provide for inpatients. Then with Dr. Bener Jones he secured influential help, including a provocative article by Charles Dickens in "Household Words," and eventually was able to form a committee to buy a house in Great Ormond Street, an area of London that had once been fashionable but where houses were "going down" as the social centre of the city moved westwards. The drawing room of the house which had seen fashionable parties became the first ward of 10 beds. Nursing staff were recruited and strict rules for the prevention of infection were drawn up. On St. Valentine's Day, 1852, the first inpatient, called Eliza Armstrong, aged 3½ years, was admitted. Charles West had started something that was to become world famous.

The rest of the story is of a hundred years of expansion in size, in staff, in scope and in fame. It is told by the senior surgeon to the hospital, Mr. T. T. Higgins, F.R.C.S., in a little volume specially prepared for the centenary year and called "Great Ormond Street, 1852—1952" (Odhams Press, Ltd., Long Acre, London, price seven shillings and six pence). Copiously illustrated, this book should be of great interest to all paediatricians. It tells of the purchase of the "house next door," the first specially built block begun in 1872, the south wing added in 1893 and the "Astor Building" opened in 1908 to cope with the ever growing attendances of outpatients. Plans for a completely new building were made between the 2 world wars. The new nurses' home and inpatient block were open by 1938. The outpatient department was started but had to wait until 1952 before a continuation could be made and now there is great activity while the first part of the final stages rises in what was the garden of the old house in Great Ormond Street.

The visiting staff of the hospital have included many famous names—after West the list includes William Jenner, Sydney Ringer, Cheadle, Gee, Barlow, Still, Poynton, Hutchison and on the surgical side Thomas Smith, Ballance, Arbuthnot Lane, Waugh, Fairbank. Perhaps even more remarkable is the number of eminent paediatricians in the English-speaking world of the last hundred years who have owed something to the training received in Great Ormond Street.

Before the coming of the National Health Service the hospital was constantly appealing for funds but it had many good friends, including Sir James Barrie who transferred all the rights in "Peter Pan" to the hospital. As a teaching institution it was able to keep its endowment funds at the taking over of the hospitals so that to-day while supported by the state the hospital is able to devote a considerable sum annually to research. The Institute of Child Health is the name of the "school" established in this form in 1946 as part of the University of London with a Chair in Child Health generously endowed by the Nuffield Foundation. Plans for an Institute building and for a model Child Welfare Centre and School Clinic are well advanced and a site has been purchased by the University adjacent to the hospital.

Celebrations have been proceeding in the last few months. H.R.H. the Princess Royal who worked as a nurse in the hospital in the first world war came during May to lay the foundation stone of the new outpatient department. There was a scientific demonstration, an "at-home" for old residents and nurses and an informal visit in July by H.M. the Queen. If this description of the first hundred years is unduly tinged with pride then it must be said that those of us privileged to work at The Hospital for Sick Children are also conscious of a sense of humility and of great thankfulness that we are able with magnificent premises, the building of which owes much to the generosity and leadership of the late Lord Southwood, to start the next hundred years at a time when developments in the whole field of medicine and more especially in paediatrics are beyond the wildest dreams of Charles West for all his great vision.

BOOK REVIEWS

Diseases of Nervous System in Infancy and Childhood and Adolescence, ed. 3, Frank R. Ford, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1952, $18.50, 1181 pp.

This is an important book and one that should be in the hands of every pediatrician. It is the only one of its kind. The new edition has appeared after 8 years, about the same space of time which passed between the first and second editions. No important changes can be recognized though it is apparent that a complete revision has been made in the material.

A detailed review of a new edition, particularly one that appears in its previous general structure is hardly in order. Importance of this book would justify the assumption that the previous edition is well known and is in the hands of many pediatricians and all others concerned with clinical practice with children. It seems wise, however, to point out that the author has assumed that the reader will refer to other works for information about the several procedures being developed to a high degree of usefulness in neurology, such as electroencephalography and angiography. It seems to this reviewer that these subjects could have been included in chapters devoted to the use of these procedures. There is ample reference to them in the subject matter presented.

Also, material could have been included about vital statistics of nervous system tumors. The high ranking frequency of both benign and malignant tumors in a total frequency of tumors in childhood would justify calling attention to this.

Superior quality of the book is the even balance and uniform treatment throughout all the chapters. Thorough and conservative discussion of every subject is outstanding. Case histories appended to many chapters enhance the clinical value of the book. The author and publisher alike should be praised for presenting this edition to the pediatric public.

Die Nervenkrankheiten (Diseases of Nervous System), G. Schaltenbrand, Stuttgart, George Thieme, 1951, DM 87., 880 pp., 538 partly colored illustrations.

Schaltenbrand is a former co-worker of Max Nonne, the Nestor of German neurology to whom this work is dedicated. The author also worked with Magnus in Utrecht and previously published very interesting observations on the tonic neck reflexes in infants. He studied under Cushing and Bailey.

Therefore, his own educational background enabled him to write from personal experience about developmental and heredofamilial disorders, preadolescent metabolic and infectious diseases of the nervous system. Consequently, this textbook contains more valuable information for the pediatrician than many other comprehensive volumes on neurology that are dealing with all age groups.

It is evident that those students who are searching for detailed instruction about toxoplasmosis or cerebellar astrocytoma will find more material in textbooks on pediatric neurology. But such books have not yet been published in the German literature of the after-war period.

Of special interest are the chapters on metabolic diseases (Gaucher, Niemann-Pick), on muscular dystrophies and on virus diseases. This book omits the technic of neurologic examination that is reserved for a special outline.

The physiopathology is not considered. The illustrations and the bibliography (American literature included) are excellent. Misprints (e.g., Langerhans instead of Langhans giant cells) should be eliminated.